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VOLUME XXVIII NUMBER 4

DISEASES

of the

CHEST

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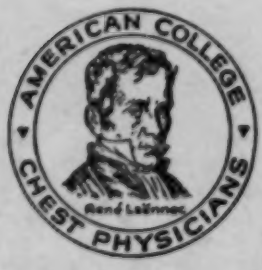

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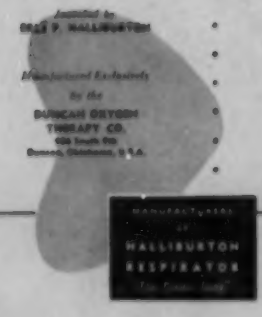

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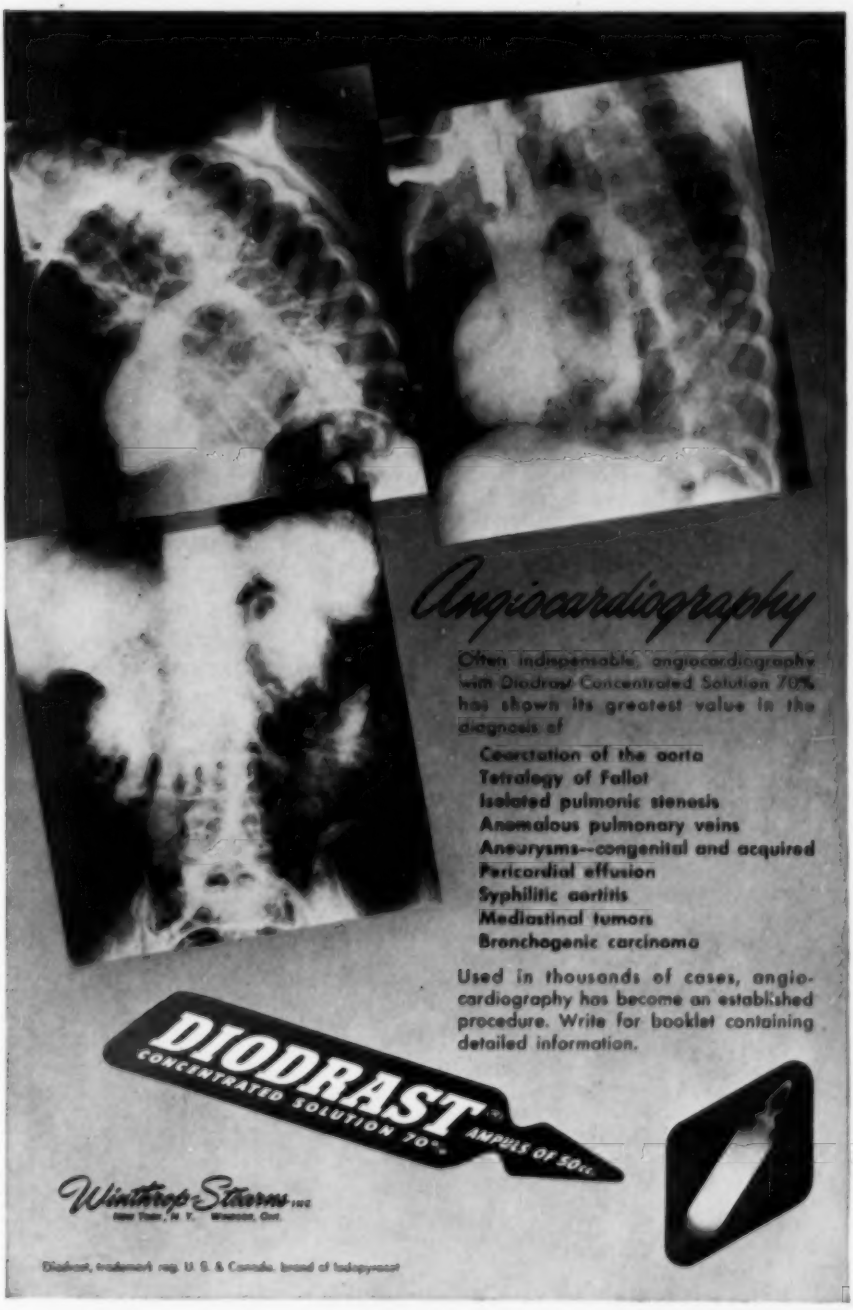
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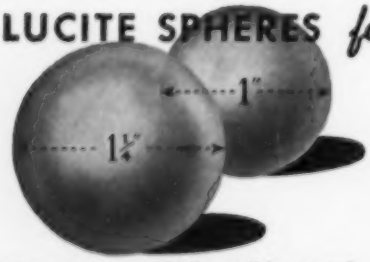

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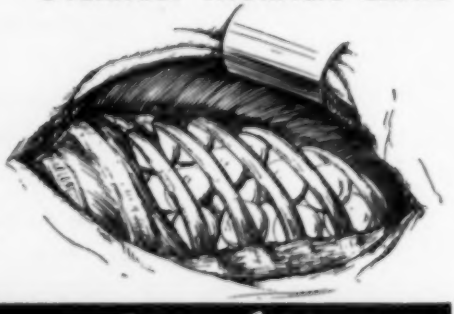

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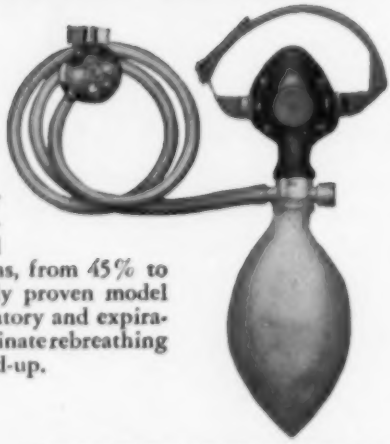

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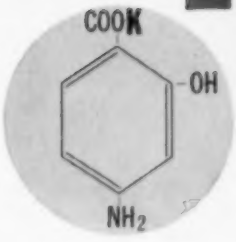

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2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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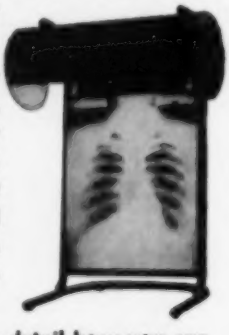

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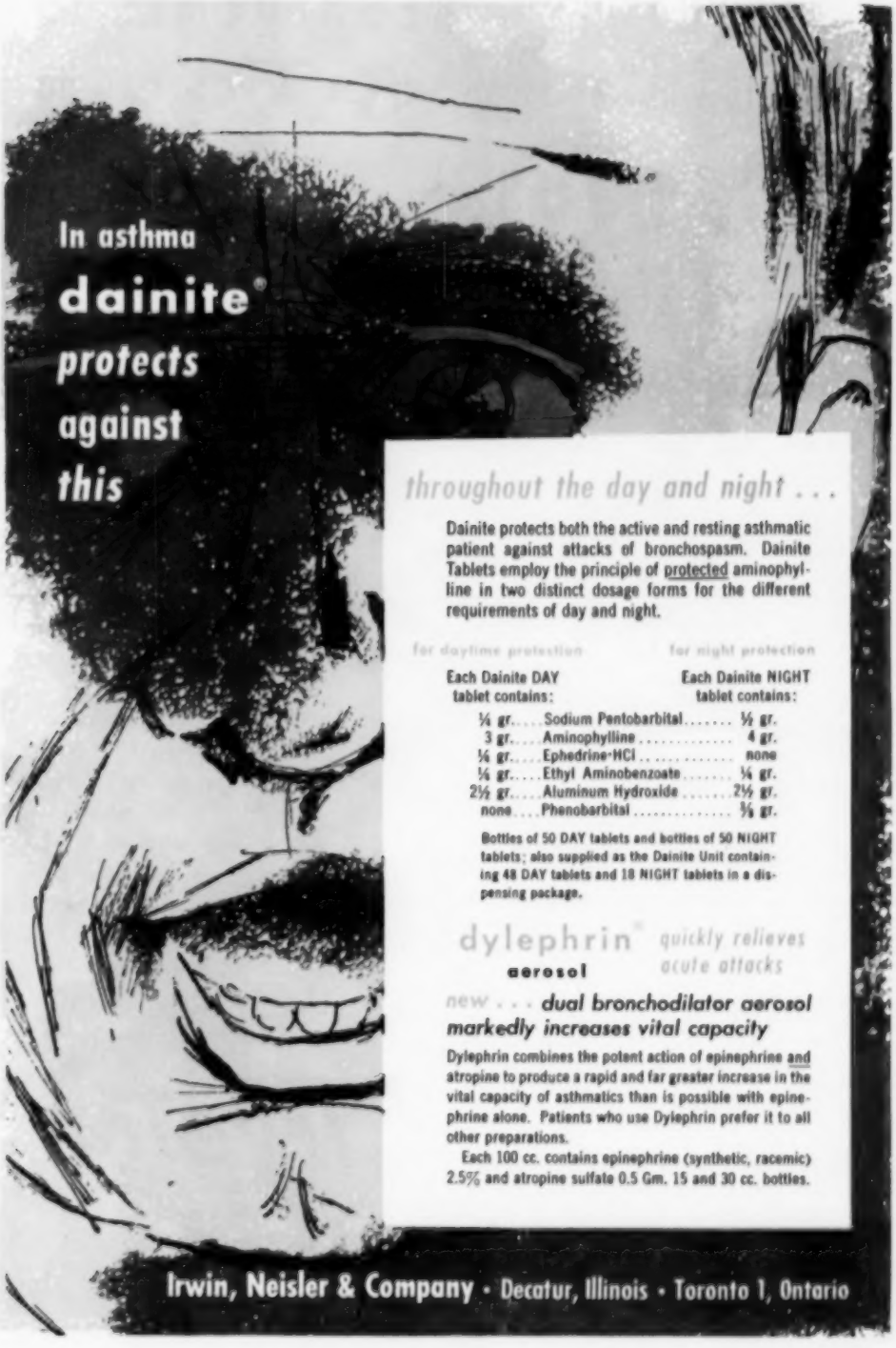

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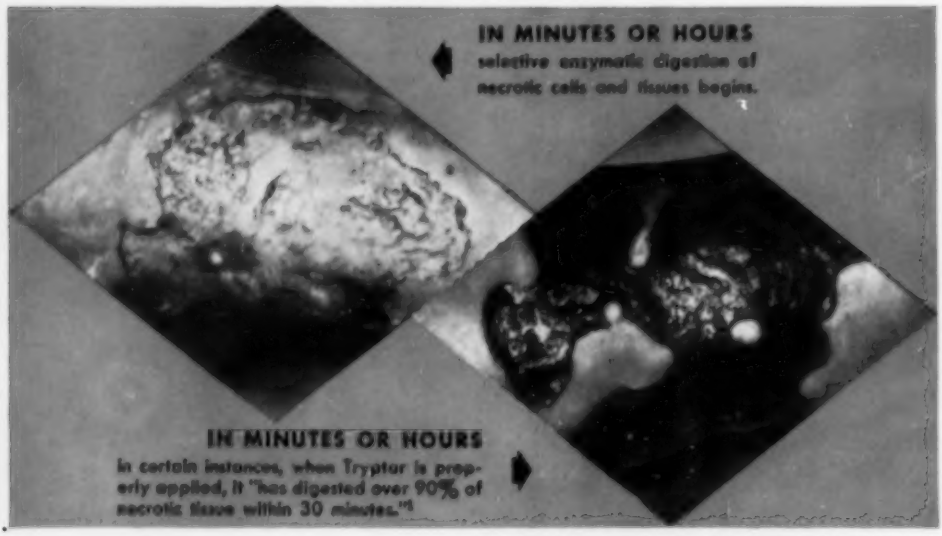
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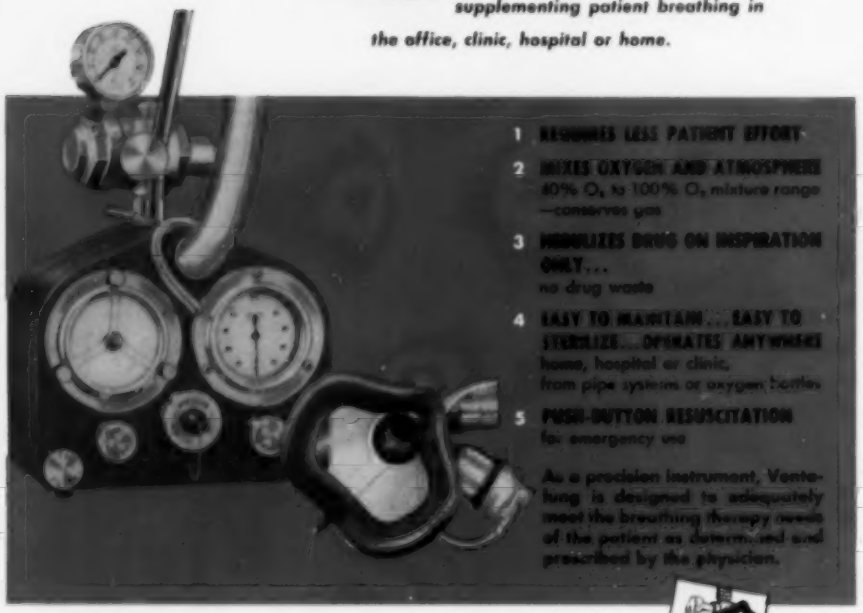
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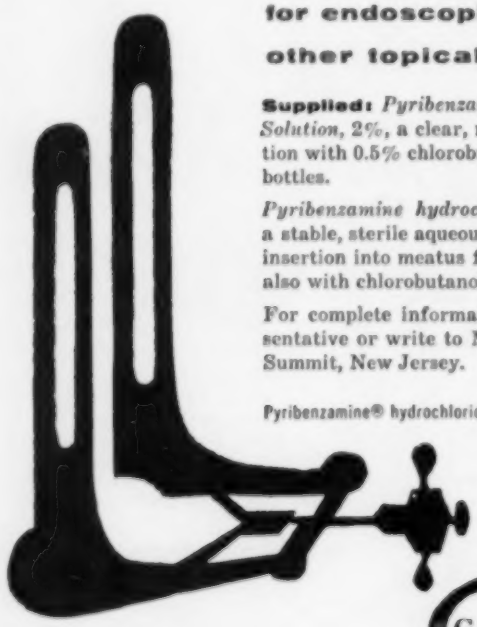

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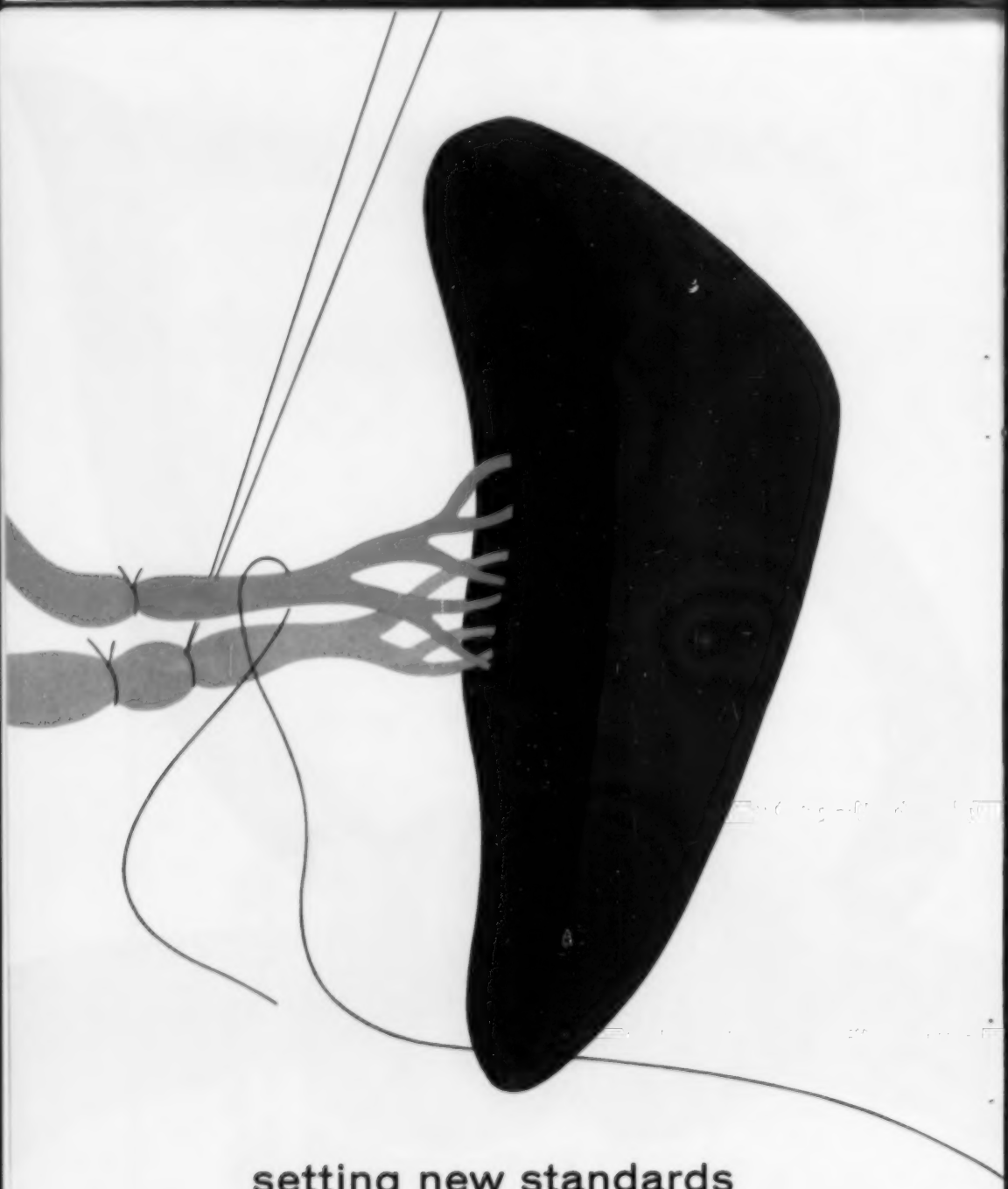

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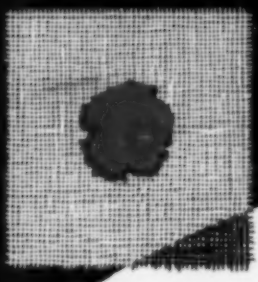

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3. Riddle, A. C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. In press.

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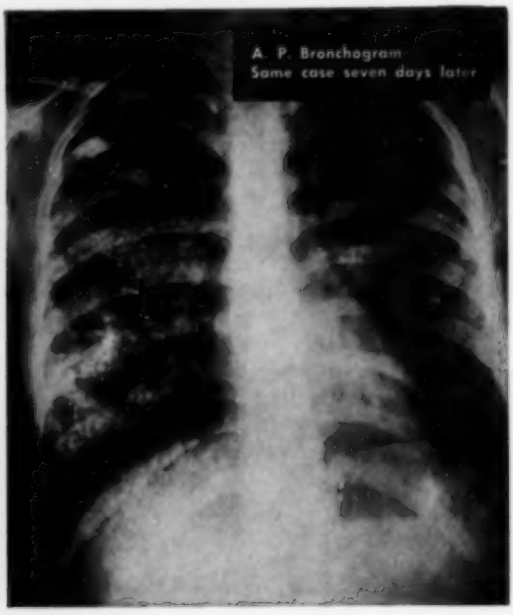

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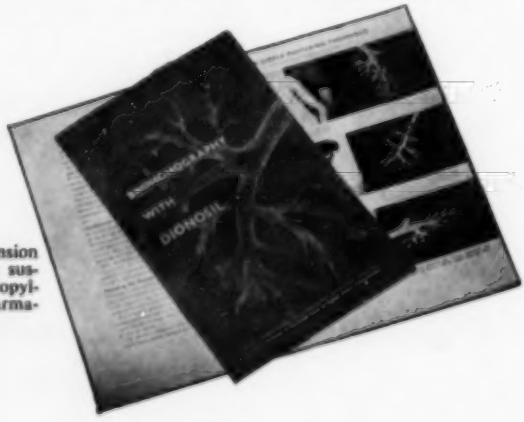

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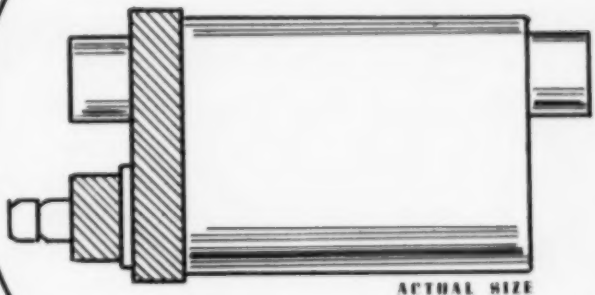

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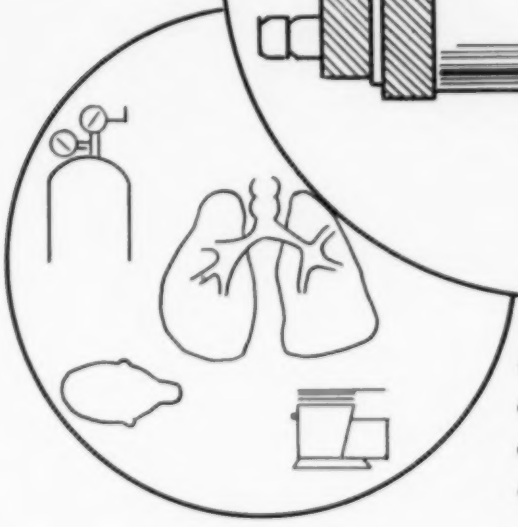

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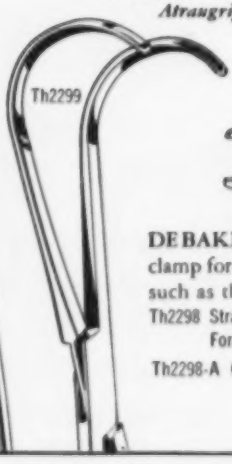

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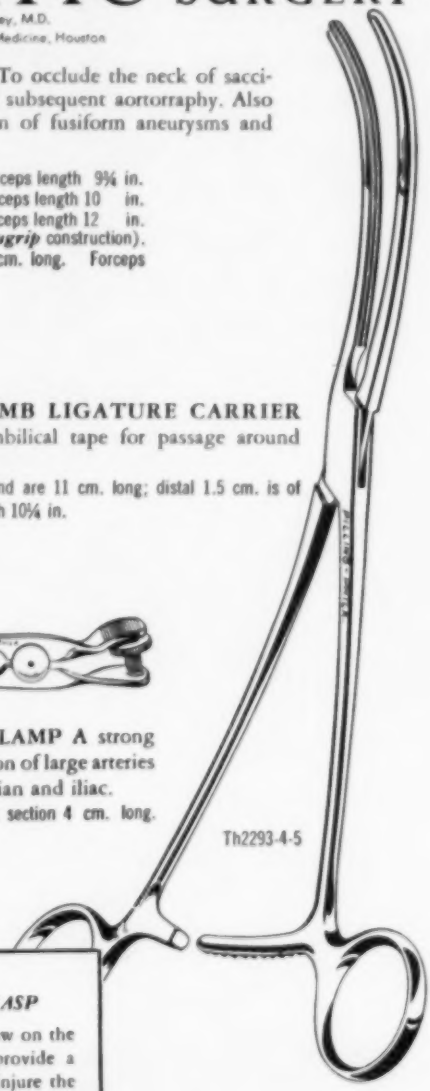

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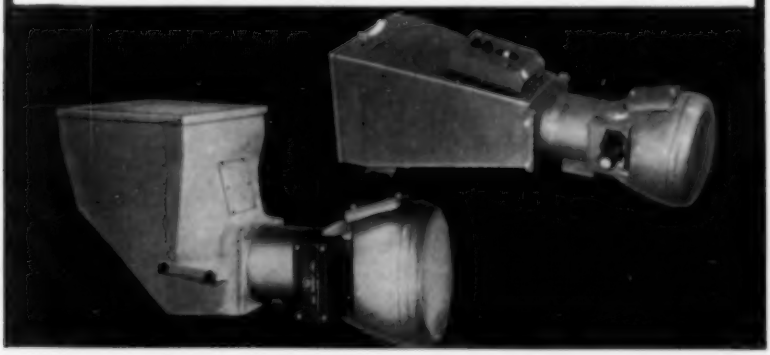

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DISEASES of the CHEST

VOLUME XXVIII OCTOBER, 1955 NUMBER 4

Arrhythmia, An Indication for Valvotomy in Mitral Stenosis; Concomitant Lobectomy for Bronchiectasis

HARRY VESELL, M.D., F.C.C.P., EDWARD J. GLUCK, M.D.
and IRVING A. SAROT, M.D., F.C.C.P.
New York, New York

Though surgical treatment for mitral stenosis was first suggested in 1902[1] and some operations were performed on mitral valves of patients as early as 1923,[2] serious and widespread concern with criteria of selection of patients with mitral stenosis for surgical treatment really began with the first successful mitral operations by Bailey and his group in Philadelphia,[3] and Harken and his group in Boston,[4] and very shortly thereafter by others throughout the world.[5]

Methods for selection of cases for mitral commissurotomy[6] have been reported by many.[5, 6] While there is not unanimity of opinion on all factors concerned, and indeed there are still some dissidents to the operation itself, there is a major agreement on many features.

In general, patients with mitral stenosis who are in Class I (functional classification of the New York Heart Association[7]) do not need the operation. Patients in Class IV, especially if well advanced, have passed the optimum time for surgery, though many can be saved and some substantially improved. Class II is a debatable area in selection. Class III is at present the one of choice.

Selection of cases now is usually based on clinical, radiological, electrocardiographic, and hemodynamic findings.[8] The mitral stenosis should be tight and pure if possible. Associated minor cardiac involvement such as mild mitral insufficiency, slight aortic valvular lesions, with no or only minimal left ventricular enlargement, do not contraindicate the operation. Associated tricuspid insufficiency often makes the indication for surgical treatment more urgent. Symptoms or signs of significant disturbance of cardiac function are a usual requirement, and if these are not severe, they should show recent progression, not due to intercurrent complications. Ausculatory findings are usually the most helpful in the diagnosis of the valve lesions. At the apex, the ffout-ta-ta-rou of Duroziez,[9] with a loud slappy first sound, a loud opening snap followed by a long rumbling diastolic murmur, with a crescendo presystolic murmur if sinus rhythm is present, and, a loud P2, form the characteristic pattern. Radio-

From the Departments of Medicine, Cardiovascular Surgery and the Cardiographic Laboratory, Beth Israel Hospital, New York, N. Y.

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logical examinations may aid, especially in locating significant left ventricular enlargement, an important contraindication, or a giant left auricle, to suggest the probability of significant mitral insufficiency.[10] Moderate systolic pulsation of the left atrial border, on the barium filled esophagus, or elicited by other methods of examination, is a variable[11] and unreliable sign[12-15] of significant and prohibitive mitral insufficiency. Calcification of the mitral valve is often readily determined. Its presence, with other indications, may make surgery more urgent, because of the probability of its increasing, and then corrective surgery would be more difficult, dangerous, or impossible. On the other hand its presence may suggest a more careful search for mitral insufficiency.[16] The use of angiocardiography as an aid in the selection of cases for surgical treatment is being developed.[17, 18]

Electrocardiographic criteria, so far, have been concerned mainly with evidence of left or right ventricular hypertrophy. Measurements of the hemodynamics formerly seemed necessary in the selection of cases[19] for surgery. Now these are performed necessarily, in only a small number of candidates,[20] about 5 per cent at one large center.[21] Pulmonary resistance, pulmonary hypertension, and pulmonary capillary pressure curves have been variously assessed[6, 22, 23, 24] as aids in the differential diagnosis and in the selection of cases. Size of the mitral valve orifice is often estimated, but calculation may be erroneous as in a recent case where the orifice was estimated as 0.6 cm.^{2} and at surgery this mitral valve was found to be perfectly normal.[8]

Little has been reported on arrhythmias in criteria for selection of cases for surgical treatment. The presence of auricular fibrillation is not considered a contraindication to valvotomy and, in one large series, 42 per cent had had this arrhythmia pre-operatively.[25] While it occurs post-operatively,[25, 26] usually ephemerally, it is of interest that many patients lose their atrial fibrillation after surgery, with or without the use of anti-arrhythmic medication. Nevertheless, atrial fibrillation has not been a consideration in the appraisal of the patient's condition for mitral commissurotomy. Atrial fibrillation is known to be detrimental to cardiac function and occasionally seriously so when it is responsible for a rapid ventricular rate or for the production of thrombi and emboli. Surgery of mitral stenosis now has a low mortality rate and morbidity. Atrial fibrillation with uncontrollable ventricular rate has been considered a contraindication to commissurotomy.[27, 28] We believe the presence of arrhythmias, such as atrial fibrillation, flutter or tachycardia may be of some importance as criteria for selection of patients with mitral stenosis for surgical treatment. We wish to describe a patient with mitral stenosis, in whom the presence of an uncontrollable, atrial flutter was a major reason for valvotomy and concomitant lobectomy was performed because of associated bronchiectasis.

Case Report: M. G., a 54 year old married white female secretary, born in the United States, was admitted to Beth Israel Hospital July 6, 1954, because of rapid heart rate. This was her fourth admission to this hospital. Her history indicated that she had had no known rheumatic fever in childhood, no joint pains, and had not been restricted in her physical activities. She had had three attacks of pneumonia

in childhood. At 22, on a medical examination preliminary to taking out life insurance, a heart murmur was first noted. About 1941 she developed a hacking cough and became somewhat short of breath, but was able to continue working regularly. Nasal polyps were removed and she received treatment by an allergist who found her skin sensitive to egg, ragweed and roses. Some improvement followed polypectomy and treatment with injection of allergens. Several electrocardiograms were taken, the last in June, 1947, and all were reported normal. About July 1, 1947, she developed some weakness and stayed at home for a few days. Increased cough with thick mucopurulent expectoration, wheezing, marked shortness of breath, and orthopnea ensued. Because of these complaints she was admitted to Beth Israel Hospital for the first time, July 17, 1947. On examination she appeared moderately dyspneic but not in acute distress. Her temperature was 101° F. Rales were heard over both lungs from the bases up to the third intercostal space posteriorly. The expiratory phase of the breath sounds was slightly prolonged. Pulmonary resonance was not impaired. The heart appeared enlarged to the left; the maximal apical impulse was felt just outside the midclavicular line. No thrill was felt. The cardiac rate at the apex was 140 per minute and completely irregular. The radial pulse rate was only 86 per minute. When the rate at the apex was slower a rumbling diastolic murmur was heard there. The blood pressure was 130/70 mm. Hg. The liver was not palpable, but the overlying area was tender. The extremities showed no edema. The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis, atrial fibrillation Class IV. E', and chronic bronchiectasis. Teleroentgenograms revealed definite enlargement of the cardiac silhouette, especially of the pulmonary artery segment. There were increased hilar pulmonary vascular markings. Urine on routine analysis was normal, as was the hemogram, except for a slight anemia. Because of the fever, chronic thick mucopurulent expectoration, pulmonary auscultatory findings, persistence of tachycardia despite rest, digitalization and salt poor diet, the diagnosis made was pneumonitis superimposed on the chronic bronchiectasis. Penicillin by injection and aerosol penicillin were given. Following combined cardiac and antibiotic therapy there was considerable improvement. The temperature became normal, dyspnea lessened, rales diminished, and the cardiac rate was reduced to 76 with pulse rate of 70 per minute. She was discharged from the hospital 17 days after admission. After a week of convalescence at home, she returned to her regular work. A salt poor diet and digitalis, 1 gram a week, were continued. In June, 1949, she had two attacks of gallbladder colic caused by gallstones revealed in x-ray films. In October, 1949, sugar was first detected in the urine. Dietary carbohydrates were reduced, and glycosuria controlled. In November, 1950, she began to have paroxysms of nocturnal dyspnea. An electrocardiogram taken November 8, 1950, revealed presence of atrial fibrillation with ventricular rate of about 80; the ventricular complexes were completely irregular; the "*f*" waves were not uniform or regular and ranged from 375 to 850 per minute. At this time injections of mercurial diuretics were started. One ml. of mercuhydrin was given intramuscularly about once weekly.

The second admission to Beth Israel Hospital was on July 15, 1951, because of pneumonitis and drowsiness. There was no ketosis however. Glycosuria and fever responded readily to treatment and she was discharged after six days.

The third admission occurred on February 17, 1952, because of bronchopneumonia. The x-ray film revealed evidence of scattered infiltrations throughout the right lower lobe. The infection responded to terramycin and she was discharged after 10 days. Because of continued marked glycosuria and loss of weight insulin was started, May 2, 1952, with 10 units of NPH insulin daily. In December, 1952, an electrocardiogram again showed the presence of atrial fibrillation. On January 14, 1953, a regular cardiac rhythm was noted for the first time in five years, during which period she had been examined at the office about once or twice a month. The electrocardiogram revealed regular upright P waves in all three standard limb leads and in V_4, at the rate of 98 per minute. Regular heart rate at 80 to 120 per minute was observed on auscultation at each of the subsequent monthly or semi-monthly office visits up to October 2, 1953, when it was again corroborated by an electrocardiogram which revealed sinus rhythm. In November, 1953, she complained of pains, and coldness of the left leg. Pulsations were not felt over the left dorsalis pedis and posterior tibial arteries. Oscillometric readings just proximal to the ankle were: left, 0 to ½ units of pulsation at 60 to 100 mm. Hg. pressure; right, 2 units of pulsation at 60 to 100 mm. Hg. pressure. Pulsations of both femoral arteries were normal. Priscoline 25 mg. every four hours was added to her other medications. After two weeks there was marked improvement with subsequent gradual and complete disappearance of the pains and increase in pulsations. This suggested that the episode might have been caused by an embolus from the left side of the heart. For the six months up to July, 1954, on the cardiac regimen described above, a diabetic diet and 25 units of NPH insulin daily, she felt well and was able to work regularly. There was a mild exacerbation of chronic bronchitis (bronchiectasis) in March, 1954. Rales were con-

stantly present at both lung bases and about four to five ounces of mucopurulent sputum were coughed up daily.

In June, 1954, after failing to adhere to the salt poor diet and the limitations on physical effort, she experienced an episode of pulmonary edema. This was treated at home. About one month later, she had a recurrence and received cedilanid, intravenously, in addition to morphine, aminophyllin, and her regular digitalis. Her heart beat continued to be 170 to 180 and therefore she was sent to the hospital, July 6, 1954. On physical examination at her fourth admission she appeared moderately dyspneic and orthopneic and had a slight cyanotic tinge to the cheeks. There was

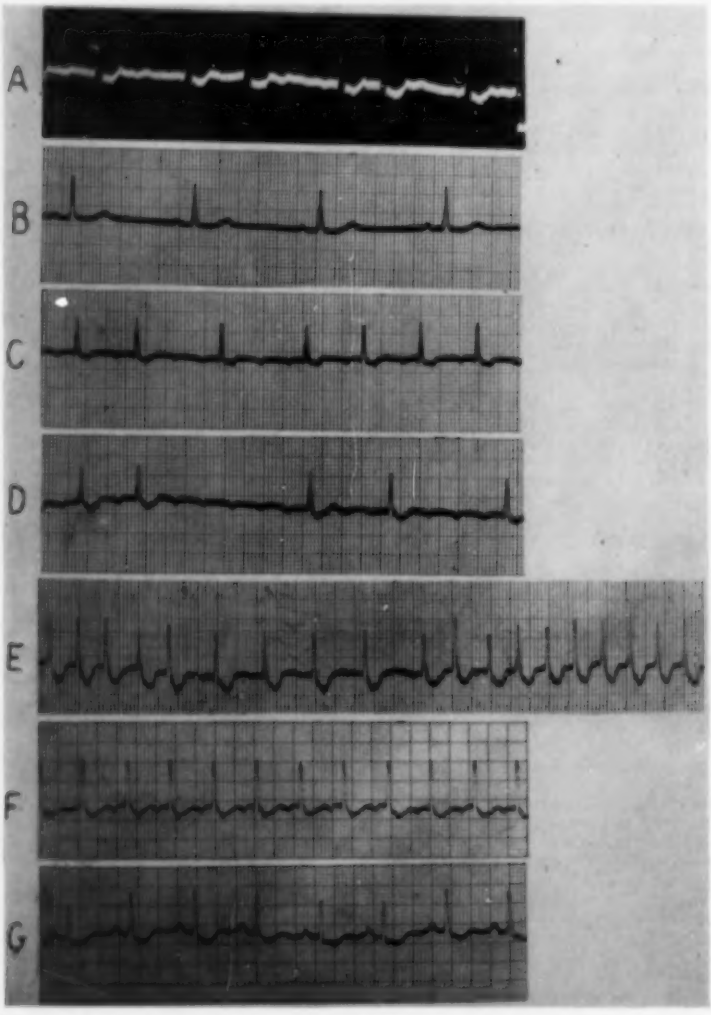

FIGURE 1: (A) Atrial fibrillation; lead CF_4; Nov. 3, 1950. (B) Regular sinus rhythm, rate 47 per minute; lead 2; Aug. 11, 1954. (C) Atrial tachycardia (flutter) 2:1 and 3:1 A-V block; lead 3; July 31, 1954. (D) Same rhythm, 6:1 A-V block after carotid sinus pressure; lead 3; July 29, 1954. (E) Atrial tachycardia (flutter), rate 115 to 187; lead 3; Oct. 2, 1954, 2 days before surgery. (F) Oct. 4, 1954, during valvotomy, 11:03 a.m., atrial tachycardia, rate 136; lead 3. (G) During valvotomy, 11:22 a.m., regular sinus rhythm, rate 94; lead 3.

cough productive of greenish yellow phlegm. The temperature was 99.8° F. The respirations were 24 per minute. The eyes, ears, nose and throat were essentially normal. She was edentulous. The thyroid was not palpably enlarged. The sublingual and neck veins (patient sitting) were distended. Wheezes and moist rales were heard throughout the lungs, more at the bases. The heart rate was about 170 per minute. When it became slower, about 110, the following heart sounds and murmurs were heard. At the apex the first sound was loud and slappy. An opening snap followed by a moderate, low pitched, rumbling diastolic murmur, louder in presystole, was heard. P_2 was only slightly increased in loudness. Later, with regular sinus rhythm and a rate of 70 to 80, the diastolic murmurs were diminished and a Grade II systolic murmur was heard at the apex. The blood pressure was 115/85. The liver was palpated two finger breadths below the costal margin. The spleen was not felt. There was slight pitting edema about the ankles. No clubbing of the toes was found. Dorsalis pedis pulsations were palpable only on the right. The diagnosis was rheumatic heart disease, mitral stenosis, probably tight, with mild mitral insufficiency; supra-ventricular tachycardia, cardiac failure, right and left sided; chronic bronchiectasis; diabetes mellitus, and cholelithiasis. A urinalysis disclosed a positive test for glucose, specific gravity of 1.010 to 1.018, and 4 to 6 white blood cells in the low power field. The hemogram was normal. Erythrocyte sedimentation rate was 57 mm. (August 9) and 30 mm. (September 8) in one hour (Westegren). The blood was sterile on culture. The electrocardiogram (July 16) revealed the presence of a tachycardia with "P" waves at a rate of 125 per minute, but with the possibility that a second "P" wave was buried in the T wave in each cycle. "P" was isoelectric, in lead 1, inverted 0.3 mm. in leads 2 and 3, upright in aVR, flat in aVL and inverted in aVF. In V_1 "P" was upright 0.5 mm., and 0.05 sec. duration, flat in V_2 to V_6. T_1 waves were not visible. The P-R interval was 0.12 sec. (VI). The electrical position was vertical, QRS being almost entirely negative in aVL and positive in aVF. S in V_2 was 20 mm., A. in V_5 was 6.2 mm. R. in V_1 was only 2 mm.; no evidence of either left or right ventricular hypertrophy. RS-T was depressed about 0.5 mm. in lead 1 and 3, and 0.8 to 1.0 mm. in lead 2, with a configuration similar to that due to digitalis. RS-T was depressed in the left precordial leads, 2.0 to 2.5 mm. in V_5 and V_6. The T wave was upright and small in the standard limb leads and flat in V_5 and V_6. Course and treatment: Her regular cardiac regime was continued. It included a low sodium diet, 200 mg., and digitoxin, which was increased to 0.2 mg. daily. No insulin was given the first few days since most of the fractional urine specimens were negative for glucose.

Treatment directed at the tachycardia included administration of quinidine up to 0.4 Gm. every two hours for five or six doses daily, omission of digitalis for 12 days, redigitalization with digitoxin 0.9 mg. followed by 0.2 mg. daily, the use of cedilanid 1.6 mg. intravenously, given in nine hours, pronestyl up to 5 Gm. daily, and potassium chloride 4.5 Gm. daily. Strips of electrocardiogram were recorded many times each day. During most of the period to August 17 the atrial tachycardia was present with P_2 and P_3 inverted. Ventricular rates were between 100 and 150, and during several short episodes 180 to 200.

The blood serum potassium, July 28 was 4.7 mEq. per liter; on August 2 the NPN was 31 mg. per 100 cc., sodium 138.4 mEq. and potassium 5 mEq. per liter. On August 25 the atrial tachycardia had been present continuously for the previous eight days, and digitalis had not been given for 28 days. It was thought a good time to test again for the possible presence of digitalis toxicity as a cause of the atrial tachycardia. The acetyl-strophanthidin test for digatalis toxicity[20] was performed. Just prior to the test the electrocardiogram revealed the presence of the atrial tachycardia with "P" inverted in leads 2 and 3, atrial rate 200, ventricular rate 120 to 135. The drug was administered intravenously, 1.2 mg., over a period of 12 minutes, with monitoring by the continuous electrocardiogram. Except for the appearance of three scattered premature ventricular beats (at two to three minutes and 0.45 mg.) no other variations were noted. Added carotid sinus massage was ineffectual. Two Gm. of quinidine had been given during the day. At 8:00 p.m. the apical rate was 100 and fairly regular. On August 26 the acetylstrophanthidin test was performed with a double dose; 2.4 mg. were given intravenously over a period of 27 minutes. There was no effect on rate or rhythm on the continuous electrocardiogram. The ventricular rate was about 140 to 170. Atrial waves were not distinguishable in the electrocardiogram before, during and just after the test. No untoward effect was observed. The results of the two tests were interpreted as failing to indicate the presence of digitalis toxicity, or that the atrial tachycardia was digitalis induced. Nevertheless treatment was continued with pronestyl 3 to 5 Gm. orally[20] and potassium chloride 4.5 Gm., per day. The atrial tachycardia persisted, with the ventricular rate between 105 and 120. By September 13 she had been in the hospital 69 days. During this time the atrial tachycardia had been continuous with the exception of about six days in the previous month. Frequent and sudden elevation of the ventricular rate to 170 to 200

was a serious threat to life. Moderately large doses of pronestyl with potassium chloride, often difficult to take, were required to reduce the ventricular rate. These drugs, also quinidine, digitalis, and prostigmine, as used, were unable to break the arrhythmia permanently or to control the ventricular rate adequately. On search for other therapy, it was thought that possibly the left atrial distention due to tight mitral stenosis, with a predisposed chamber, might be an important contributing cause to the disturbance of cardiac rate and rhythm. Its relief by surgery then seemed rational. After a day at home she returned to the hospital September 14 to be evaluated more completely for mitral commissurotomy, and prepared for the surgery, if feasible. By fluoroscopy and x-ray film the cardiac silhouette showed prominence of the pulmonary artery segment. On the barium filled esophagus the impression of the left atrium indicated moderate enlargement. There was only slight systolic pulsation of the left atrial border. The right ventricle was thought to be enlarged. The auscultatory findings were as previously described and diagnostic of mitral stenosis. The cardiac symptoms even prior to the tachycardia, if due to the mitral stenosis, strongly suggested the presence of marked narrowing of the mitral orifice. The diabetes required 20 units of insulin before and in the early part of her present hospital stay. On the hospital diet, and with her loss of weight, the insulin requirement became less and from August 22 on, insulin was omitted. Sugar in the urine was recorded as a trace or zero, and acetone was never found. The patient's temperature did not rise above 99.8° F. with the exception of one brief episode of fever, July 17 and July 18, which disappeared after several injections of Dicrysticin. About five ounces of greenish yellow mucopurulent sputum continued to be produced daily. Culture of this showed occasional streptococcus viridans, non-hemolytic streptococcus and micrococcus catarrhalis. Active rheumatic fever as a possible cause for the cardiac arrhythmia had been carefully considered. The antistreptolysin titer was elevated; 100 units on September 20, 1000 units on September 24 and 700 units on September 30. As a therapeutic test and for possible beneficial effect, cortisone, 75 mg. daily for two weeks, was given (September 22 to October 4) but failed, at this dosage, to influence the auricular tachycardia. A bronchogram, on September 30, with Dionosil, revealed the presence of extensive saccular bronchiectasis in all segments of both lower lobes, more severe on the left. The lingular bronchus of the left upper lobe and the right middle lobe bronchus did not fill completely. Because of the pulmonary findings it was thought that left lower lobectomy might be done at the time of commissurotomy. Consent for this additional procedure was obtained from the patient. From September 14 to 25, while being prepared for surgery, the patient continued to receive pronestyl, 3.75 to 5.0 Gm. by mouth daily, except on September 20, when only 2 Gm. were taken; also potassium chloride 4.5 Gm. daily. There were frequent rises in the ventricular rate to about 140 per minute and on September 25 the apical rate rose to 200. Digitoxin was then restarted; none had been given for one month, since August 26; 1.2 mg. were given orally in 48 hours, then 0.15 mg. daily; pronestyl 5 Gm. daily and, because of some dyspnea, the mercuhydrin, 1 cc., was increased in frequency to daily for three days. In six hours the ventricular rate slowed to 108 to 120. However on October 2 it was 200 once more. Prostigmine in doses of 0.25 mg. and 0.5 mg. was given to a total of 3 mg., but the apical rate remained between 130 and 180. On October 4, the morning on which the operation was scheduled, her cardiac rate, even after pronestyl 750 mg., prostigmine 0.5 mg. and seconal 0.2 Gm., was 140 to 150. The anesthesiologist was reluctant to begin. However, since a rapid heart rate (160 to 200) had been present for two days almost continuously, and since it was for the elimination of this tachycardia that the surgery was in large part being urged at this time, since cardiac failure was still minimal with the probability of increase, and since there had been several days of considerable surgical preparation, it was decided to start the anesthesia and proceed with the operation. The heart rate and electrocardiogram were continuously observed on the cardioscope.

Operation (I. A. S.): The patient was placed on the table in the left lateral position with the head and chest somewhat elevated. The chest was opened through an incision in the periosteal bed of the fifth rib. The anesthesiologist had been having difficulty because of the large amount of sputum emanating from the left lower lobe. The left lower lobe bronchus was exposed promptly and clamped after ligation and division of the pulmonary artery branches to the lobe. Following this there was no difficulty with secretions. On the cardioscope the ventricular rate was recorded as 140 to 150 per minute, with atrial tachycardia, and P_2 and P_3 inverted. The blood pressure was between 80 and 100 systolic. At about 11:20 a.m. the phrenic nerve and vessels were mobilized and the pericardium incised. There was a sudden reversion to regular sinus rhythm with a drop in rate to 95; the blood pressure promptly rose to 120 systolic with concurrent improvement in the color of the tissues. There was a marked diastolic thrill at the apex of the left ventricle. The left atrium was greatly enlarged. Old organized clot was present in the atrial appendage. A systolic regurgitation jet of moderate degree was present and palpable. The posterior leaflet (mural) of the mitral valve contained much calcium in its edge and was thickened and shrunken. The mitral orifice was

a slit like structure which could be opened easily and admitted one and a half fingers. But the super position of the edge of the posterior leaflet caused an increase in the stenosis functionally. The anterior lateral commissure was cut and then digitally fractured to the muscular wall. The short posterior medial commissure was not cut. At this point the diastolic thrill at the apex of the heart had disappeared. The left lower lobectomy was then completed. Except for one minute, about 13 minutes after its cessation, the atrial tachycardia did not recur throughout the rest of the operation, a period of about 90 minutes, and the cardiac rate did not exceed 120. The post-operative reaction was not unduly severe. The patient received oxygen by nasal catheter; 1000 cc. of blood by slow intravenous infusion were given over a period of

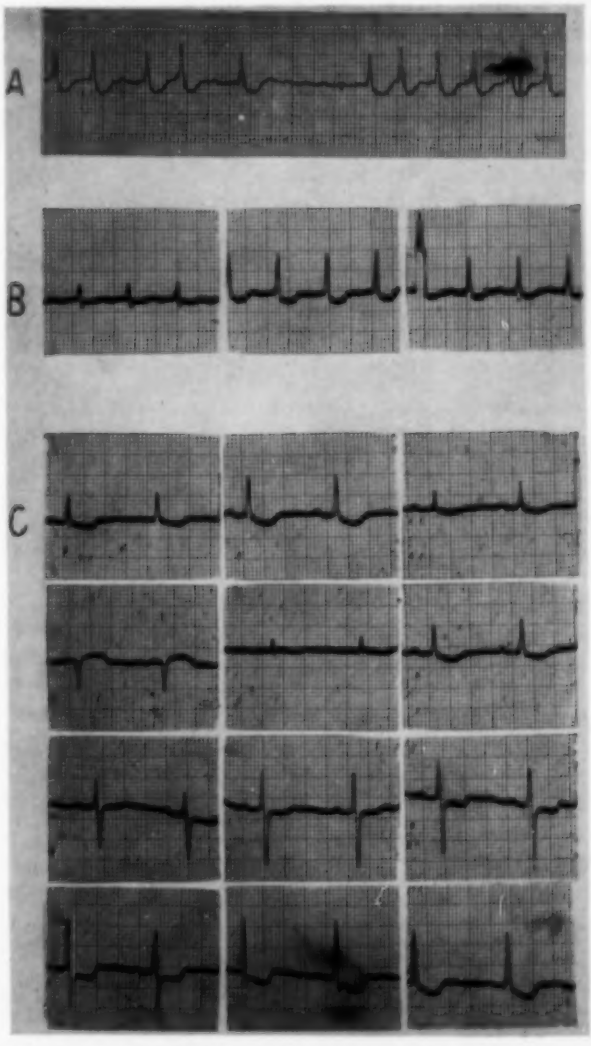

FIGURE 2: (A) Oct. 6, 1954, 48 hours after operation; episode of atrial tachycardia, P waves upright, lead 3; no subsequent episodes with such rapid atrial rate. (B) from left to right, leads 1, 2 and 3. Sinus tachycardia, rate 125, upright P in lead 3. (C) Nov. 23, 1954, 50 days after operation. From left to right, leads 1, 2, 3, aVR, aVL, aVF, V_1, V_2, V_3, V_4, V_5 and V_6. Regular sinus rhythm, rate 70; digitalis effects.

six hours. There was some difficulty in expectorating and coughing, and large amounts of purulent material were obtained at each suctioning. At 3 hours after operation the heart rate was 112. Twenty four hours later she "dangled" off the edge of the bed for 10 minutes; the heart rate was 120, respirations 20, and blood pressure 114/80. Forty-eight hours after operation there was an episode of tachycardia with an atrial and ventricular rate of 160 to 170 per minute. The electrocardiogram (Fig. 2A) showed this to be different from the preoperative tachycardia in that P_2 and P_3 now were upright and not inverted. Medication administered had to be given parenterally. Acetyl-strophanthidin, quinidine gluconate, benedryl and amytal were given over a period of several hours. Slowing of the heart rate occurred during the night, and the next day there was a regular sinus rhythm with a rate of 84 per minute. By October 19 (15 days after operation) the patient showed signs of considerable improvement; the cyanotic tinge to the cheeks was no longer present; the cardiac rate was 80 and regular; the cardiac sounds had changed from before surgery. The first sound at the apex was less accentuated; the opening snap and diastolic murmur were not heard. A grade 1 to 2 (6 maximum) systolic murmur was present; P_2 was not accentuated; there was no evidence of venous hypertension, sublingual and neck veins were not unduly filled. Rales were present at the right lung base, and about ½ to 1 ounce of sputum was expectorated daily. For the three weeks up to the time of her discharge from the hospital (November 17), her temperature was normal, though the ESR on November 3 was still elevated, 57 mm. For a few hours on October 11 and October 28 there was an increase in cardiac rate to 130 and 170 per minute, respectively, but the electrocardiogram revealed P waves in lead 2 and 3 to be upright. After her return home the digitoxin was continued at 0.1 mg. daily, quinidine 0.2 Gm., three to four times daily; the diet was moderately restricted in sodium. Restrictions on physical activity were slowly removed. There were several episodes, each of a few minutes to about one hour, of increase in cardiac rate, which the patient felt and made note of. The heart rates at the apex taken then by the patient and doctor were about 100 to 120. In two of these periods the electrocardiogram was recorded and revealed a regular sinus rhythm with upright P waves in all standard limb leads. She returned to her regular work on January 13, 1955, 100 days after the commissurotomy and lobectomy, and up to the time of writing, two months, has been working regularly. During this period there has been no recurrence of the atrial tachycardia chiefly for which valvotomy was undertaken.

Pathological Findings

The specimen of atrial appendage (posterior) was 2 x 2 x 0.7 cm. The endocardial surface was smooth and glistening. No Aschoff bodies were seen. Left lower lobe of lung with 2 cm. of main stem bronchus, measured 18 x 7 x 2.5 cm. and weighed 150 Gm. The pleural surfaces were smooth and glistening over the entire posterior surface except where there were fibrous strands adherent to the pleural surface; this was most marked over the posterior basal surfaces. The anterior, posterior and lateral basal branch bronchi were all dilated and filled with viscid white secretions. They could be traced to the periphery. The pulmonary arterioles showed considerable thickening of the musculature and some narrowing of the lumen. The smaller arteries also had considerable hypertrophy of the muscular layer and subintimal deposition of lipid material. There was some thickening of the alveolar septa.

Discussion

There were several unusual problems in diagnosis and treatment of mitral stenosis in the case described above:

1) separation of certain symptoms and signs of mitral stenosis and cardiac failure, from those of chronic bronchiectasis,

2) estimation of the tightness of mitral stenosis,

3) the nature and cause of arrhythmia,

4) the treatment of the cardiac and pulmonary conditions.

The patient had been observed over a period of seven and a half years,

during which time increase of the cardiac and pulmonary symptoms and signs were noted. Progression of the cardiac disease was seen in the gradual increase in the shortness of breath and orthopnea, the development of paroxysmal nocturnal dyspnea, venous hypertension, enlargement of the liver and slight edema about the ankles. Treatment with digitalis, periodic mercurial diuretics and sodium poor diet was necessary and helpful during the last few years. Bronchitis is common in tight mitral stenosis.[12, 31, 32] The diagnosis of chronic bronchiectasis, however, was based on several features: history of several attacks of pneumonia during childhood, and also later; chronic hacking cough since childhood, with the production of four to five ounces of mucopurulent sputum daily for many years. This diagnosis was established by the bronchogram, corroborated at surgery, and finally by the gross and microscopic examination of the lung removed at operation. Chronic bronchiectasis undoubtedly was responsible for much of the cough, the expectoration, and some dyspnea; also for most of the rales heard over both lungs many years, for in spite of the many rales there was often little or no dyspnea and the patient was able to work regularly. The bout of fever early in the last hospital stay subsided promptly with antibiotic therapy, as did several such previous bouts, and therefore seemed caused by the pulmonary infection. Elevated sedimentation rate, antistreptolysin titer and fever, need not be due to rheumatic activity.[33]

The diagnosis of tight mitral stenosis was based upon several features. Important in this diagnosis was the onset of pulmonary symptoms due to the cardiac lesion. The pulmonary manifestations of "tight, non-regurgitant" mitral stenosis were reported from this hospital almost 25 years ago by Held and associates.[34] Frequent pulmonary infections, bronchopneumonia, also chronic progressive pulmonary symptoms may be prominent, and in the past have led to the diagnosis of tuberculosis and pulmonary neoplasm.[30, 35] Similar pulmonary manifestations were present in our case over the period of a few years but were difficult to separate from those of the chronic bronchiectasis. The acute pulmonary symptoms of tight mitral stenosis were clearly described and explained by McGinn and White[36] more than 20 years ago. These acute pulmonary symptoms, pulmonary edema, cardiac asthma or hemoptysis, occurring with physical effort or its equivalent, and due to acute left atrial failure behind a tight and obstructive mitral orifice, therefore have been referred to by us for years as the "McGinn and White" syndrome. Asthmatic-like attacks and pulmonary edema associated with effort or tachycardia, did occur in our patient. Thus the presence of both these chronic and acute pulmonary manifestations strongly suggested that if due to mitral stenosis the orifice was narrow.[6] The auscultatory "ffout-ta-ta-rou" rhythm was considered pathognomonic of the presence of mitral stenosis by Duroziez.[9] With the loud and slappy apical first sound, with a moderately loud opening snap, a long loud mid-diastolic and a "presystolic" murmur it further suggested that the stenosis was marked.[10] The absence of a loud P_2 usually associated with pulmonary congestion or pulmonary hypertension[10] has been

noted.[37, 38] P_2 was only mildly to moderately accentuated, grade 2 (6 maximum). The frequently noted absence of a systolic murmur at the apex together with absence of evidence of notable enlargement of the left ventricle in the electrocardiographic and roentgenographic studies, and the absence of marked ventricular systolic pulsation of the posterior left atrial border in the fluoroscopic examination[11] all pointed to the presence of little or no mitral insufficiency. Mild to moderate ventricular systolic pulsation of the posterior left atrial border, we and others[6, 39] have found when no systolic jet was noted at surgery. We believe mild to moderate systolic pulsations of the left atrium may result from the ambient ventricular systolic commotion of the heart and large blood vessels, even in the absence of valvular lesions, especially with the vertically positioned heart.[40] Bramwell[41] has emphasized the importance of distinguishing expansile pulsation of the left atrium from backward displacement of the left atrium by an hypertrophied right ventricle, which he says may occur in pure mitral stenosis. Bulging of the mitral valve with ventricular systole has also been mentioned as a cause of left atrial pulsations.[15] The significance of the absence of large ventricular systolic pulsations of the posterior left artial border in ruling out marked mitral insufficiency remains to be better evaluated. Esophageal piezocardiograms have been considered helpful in differential diagnosis.[42] The arrhythmia described above, commonly called atrial flutter, because of the A-V block, is closely related to atrial fibrillation[43, 44] and therefore the latter has also been considered in the discussion. It can also be classified[44] as atrial tachycardia, with a rate of about 200, a caudad pacemaker, without T_a waves and with frequent 2:1 and greater A-V block, and occasional 1:1 response. Recently it has been shown that atrial tachycardias are commonly due to digitalis toxicity, and that concomitant disturbances of the body electrolytes, potassium and sodium, may play a role in their production.[29] Several attempts at evaluation of such an etiology were undertaken and included abstinence from digitalis for long periods, administration of potassium and pronestyl and finally the tests with acetyl strophanthidin. The patient's type of atrial tachycardia of long duration, with the caudad focus and almost no extrasystoles, was not the one usually found in the Lown and Levine group[29] due to digitalis. The results in our trials failed to establish digitalis as the cause of the arrhythmia in our case. The sudden cessation of the arrhythmia during surgery and its continued absence thereafter despite the administration of full doses of digitialis also favor a non-digitalis origin.

Consideration of rheumatic activity as the cause of the arrhythmia was obligate. The nature of this primary disease,[45] the elevated sedimentation rate, cardiac failure and also the high antistreptolysin titer were in its favor. It has been mentioned previously that an elevated erythrocyte sedimentation rate and antistreptolysin titer need not be regarded as positive evidence of rheumatic activity.[33, 46] Many features of the case made one doubt active rheumatic fever the cause of the arrhythmia[46, 47]: the patient's age,[48] 55 years; the long afebrile period during

this arrhythmia; the absence of joint symptoms; the periods with sinus rhythm and normal or slow cardiac rate, both atrial and ventricular, without digitalis; the normal Q-T interval. A therapeutic trial with cortisone, 75 mg. a day for 10 days also failed to influence the arrhythmia. Additional evidence later was the absence of Aschoff bodies or other anatomical evidence of fresh rheumatic activity in the biopsied atrial appendage and in the lung removed. The sudden cessation of the atrial tachycardia immediately with the cardiac surgery, and its continued absence from then on to the time of writing, five months later, also seemed evidence against the presence of fresh rheumatic activity as the cause of the arrhythmia. The mechanism and cause of the arrhythmia were not clear. As a contributory cause, mechanical distention of the left atrium and pulmonary veins was thought of.[43] It had been a common belief that many irregularities of the heart were due to overdistention of its chambers, especially that fibrillation of the atria may so be produced.[43] It was postulated that in a predisposed rheumatic left atrium, distention of the left atrium and pulmonary veins, directly, or through presso-receptors here with efferent connections to right and left atria, might be responsible. On the grounds that by lessening of atrial distention there would be reduction of stimuli through such a reflex nervous mechanism and so possible cessation of the arrhythmia, and also by improvement of cardiac function after reduction of obstruction of the tight mitral valve by valvotomy, there might be improvement of circulation to the atrium, this operation was recommended.

The reasons for starting with the surgical procedure in spite of the presence of the arrhythmia with an uncontrollable, rapid ventricular rate are mentioned above. The ventricular rate of 136 to 150 continued during the induction of the anesthesia, chest incision, and opening of the chest wall and deflation of the lung. A growing trend toward less fear of arrhythmias occurring during surgery[49, 50] encouraged continuation of the operation with careful cardiographic monitoring. When the left phrenic nerve was displaced and the pericardium over the left atrium and in the proximity of the superficial cardiac plexus manipulated, cardiac rhythm suddenly reverted to normal with an atrial and ventricular rate of 95 per minute. The atrial appendage was promptly opened and the orifice of the tight mitral valve was enlarged to two finger-breadths by finger fracture of the anterior lateral commissure. After presence of the arrhythmia for three months in spite of considerable medical treatment for its elimination, its cessation during cardiac surgery directed at its removal, and its continued absence for five months, up to the time of writing, strongly suggest a causal relation between the surgery and this result. The exact mechanism of termination of the arrhythmia is not clear. Its sudden end during operative manipulation in the region of the phrenic and cardiac nerves, and its absence thereafter, suggested reflex action through direct stimulation of the cardiac nervous apparatus aided by reduction of stimulation due to lessening of left auricular distention.[51] Ligation of the left lower bronchus with division of pulmonary artery branches

may have contributed to the conversion of rhythm through reflex action via the vagus.[52] It is well know that vagal stimulation may convert atrial flutter to normal action.[53] In addition to these more direct vagal actions, indirect vagal stimulation through stretch receptors of the atria may be concerned. The atrial presso-receptors have recently received careful study by Whitteredge[52] and Paintal[54] and increase of pressure within or distention of the atria was shown to send stimuli over the cervical vagus nerve. Paintal has located receptors for stretch stimuli in both atria; in the left posteriorly, some near the opening of the veins.[54] Though their function was obscure, he found the impulses were carried through the vagus nerve. Scherf has recently reported[55] production of atrial fibrillation in one animal experiment when the atrial (right) wall was stretched after cooling, though cooling alone in this one experiment did not cause the arrhythmia. While the explanation of the exact mechanism of the arrhythmia in our case and of the manner of its cessation are speculative, it is factual that it did stop with the cardiac surgery and thereafter. Of considerable importance, is the concept that an uncontrollable arrhythmia with a rapid cardiac rate need not be a contraindication to valvular surgery. But, it appears, as in this case, mitral valvotomy may even be effective in helping to terminate the arrhythmia and so be an additional indication for such surgery, in the presence of other suitable conditions. After conversion of the arrhythmia there was improvement in the patients general condition, ventricular rate and blood pressure. The lobectomy was then completed without difficulty. Combination of left lobectomy and valvotomy has been reported recently by Bailey[56]; also right lobectomy for carcinoma of the lung combined with valvotomy for mitral stenosis, has been reported by Shaw,[57] and Bailey.[56]

SUMMARY AND CONCLUSION

1. A 55 year old woman with rheumatic mitral stenosis and chronic bronchiectasis developed atrial tachycardia (flutter) with rapid ventricular rate. This arrhythmia was uncontrollable though considerable treatment with antiarrhythmics, other cardiac drugs, therapy for digitalis intoxication, and antirheumatic treatment had been tried, over a period of three months.

2. On the possibility that distention of the left atrium due to tight mitral stenosis might be contributory in production of arrhythmia, probably through stimulation of stretch receptors and reflex vagal action, reduction of this distention by mitral valvotomy was recommended.

3. The three month old arrhythmia stopped suddenly during surgery, while cardiac neural structures were manipulated just prior to the dilatation of the tight mitral valve.

4. Arrhythmia has remained absent up to the present time, five months after surgery, and the patient improved greatly and has been working regularly for the past two months.

5. Concomitant lobectomy of the left lower lobe, for chronic bronchiectasis, was performed with the valvotomy.

6. This experience would suggest that an uncontrollable arrhythmia need not be a contraindication to mitral valvotomy, and in a suitable case may be an additional indication for it.

RESUMEN

1. Una mujer de 55 años con estenosis mitral reumática y bronquiectasia, presentó taquicardia atrial (flutter) con aceleración ventricular. Esta arritmia fué incontrolable aunque se emplearon antiarrítmicos en consideración así como otras drogas cardiacas, tratamiento para la intoxicación digitálica y tratamiento antirreumático por más de tres meses.

2. Ante la posilibidad de que hubiese distensión del atrio izquierdo debida a acentuada estenosis como factor que contribuyese a la arritmia, probablemente por estimulación de los receptores a la distensión y por acción vagal refleja, se recomendó la reducción de esta distensión por valvulotomía mitral.

3. La arritmia de tres meses de duración se detuvo durante la operación mientras se manipulaban las estructuras neurales cardiacas justamente antes de la dilatación de la válvula estrecha.

4. La arritmia no ha vuelto a presentarse hasta ahora, cinco meses después de la operación y la enferma mejoró grandemente y ha estado trabajando regularmente durante los últimos dos meses.

5. Al mismo tiempo que se hizo la valvulotomía, se realizó lobectomía inferior izquierda por bronquiectasia.

6. Esta experiencia sugeriría que una arritmia incontrolable no es necesariamente una contraindicación ara la valvulotomía mitral y que en un caso adecuado podría precisamente ser una indicación para ella.

RESUME

1. Une femme âgée de 55 ans, atteinte de rétrécissement mitral d'origine rhumatismal associé à une dilatation des bronches chronique, fut atteinte d'un flutter avec accélération considérable du rythme ventriculaire. On ne parvint pas à faire cesser cette arythmie malgré un effort considérable de traitement avec les régulateurs du rythme cardiaque et toutes les médications cardiaques habituelles, le traitemnt de l'intoxication digitalique, et le traitement anti-infectieux contre le rhumatisme. Ces essais furent poursuivis pendant trois mois.

2. On envisagea alors la possibilité que la distension des cavités droites en rapport avec la sténose mitrale serrée puisse jouer un rôle dans la production de l'arythmie vraisemblablement par une stimulation des terminaisons nerveuses, et par l'action d'un réflexe neurovégétatif. On envisagea alors la distension de l'orifice par une valvulotomie mitrale.

3. Cette arythmie qui durait depuis trois mois s'arrêta soudain au cours de l'intervention, alors que l'on atteignait les centres nerveux cardiaques exactement avant que l'on procédât à la dilatation de la valvule mitrale.

4. Jusqu'à présent, cinq mois après l'intervention, l'arythmie ne se reproduisit pas, la malade est très améliorée, et depuis deux mois a repris un travail régulier.

5. Au cours de cette intervention sur la valvule mitrale fut réalisée la lobectomie simultanée du lobe inférieur gauche, qui était atteint de bronchiectasie.

6. Cette expérience permet de penser qu'une arythmie résistante à la thérapeutique ne doit pas êtr considérée comme une contre-indication à la valvulotomie mitrale. Il est même possible que dans des cas déterminés, elle puisse en réaliser une indication supplémentaire.

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Bacteriophage Susceptibility and Cultural Characteristics of BCG and Other Tubercle Bacilli*

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In the course of investigations on the colonial morphology of different strains of mycobacteria,[1] their susceptibility to recently isolated bacteriophages[2] and physiological properties associated with pathogenicity, it was observed that several strains of BCG in the Olive View culture collection showed some differences from each other by the various technics employed. In order to determine if these or other variations were of frequent occurrence, a larger number of cultures of BCG was therefore obtained for further investigation from laboratories known to be working with this organism in various parts of the world.

The source and history of all cultures are recorded in Table I. The well-known pathogenic human organism, H37 Rv, and its non-pathogenic variant, H37 Ra, the so-called "moderately virulent" human isolate, R1 Rv, and a pathogenic organism of bovine origin, Corper, were also included in these studies as controls of technics and pathogenicity.

Cultural Studies

Jensen recently stated that "only by working with the same media year after year it is possible to obtain sufficient experience to make the differential diagnosis on the basis of the morphology of the colonies and other characteristics of growth without resorting to inoculation of guinea pigs."[3] During the past five years, a bacteriologic study of over 700 cultures of acid-fast bacilli of all types, pathogenic and saprophytic, has shown that differentiation and characterization of these cultures was facilitated by repeated transfer on a variety of media. This corrects for minor variations in appearance from subculture to subculture due to slight, not easily measured changes in moisture content and age of the medium and inoculum, oxygenation, temperature, medium composition and other factors. Some cultures appearing similar on a single medium, particularly egg media, were sharply distinguished by their growth on other media utilized. In addition, the appearance of true mutations are more apt to be observed.

For these studies, the following media were used:

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TABLE I

SOURCE AND HISTORY OF CULTURES

BCG Code No.	Strain	Received from	Source	Previous History Interval (days)	Media*	Used for** Vaccine
1	BCG A-178	Birkhaug, Albany	Guerin, 1946	14	P	0
2	BCG 764	Van Deinse, Paris	Calmette	14	B	0
3	BCG 994 Ser2	Van Deinse, Paris	Calmette	14	P	0
4	BCG 888	Van Deinse, Paris	Calmette	14	P	0
5	BCG 805 Ser2	Olive View	Birkhaug, 1950	90	E, T	—
6	BCG 26	Olive View	Aronson, 1950	90	E, T	—
7	BCG	Olive View	Suhrland, 1949	90	E, T	—
8	BCG	Olive View	Smith, 1950	90	E, T	—
9	BCG	Olive View	Rosenthal, 1948	90	E, T	—
10	BCG 968	Olive View	Tolderlund, 1952	90	E, T	—
11	BCG 969	Olive View	Tolderlund, 1952	90	E, T	—
12	BCG 976	Olive View	Tolderlund, 1952	90	E, T	—
13	BCG 974	Olive View	Tolderlund, 1952	90	E, T	—
18	BCG 54-126	Leon, Mexico	Van Deinse	4	P, B	+
19	BCG 826	Aronson, Philadelphia	Vorwald, 1950	30	P	0
21	BCG 275	Aronson, Philadelphia	Boe, 1948	30	P	0
23	BCG B178	Aronson, Philadelphia	(Sweden), 1950	30	P	0
24	BCG 978	Aronson, Philadelphia	Tolderlund, 1949	30	P	0
25	BCG 1	Aronson, Philadelphia	Wassen, 1951	30	P	0
26	BCG 118	Aronson, Philadelphia	(Denmark), 1952	30	P	0
27	BCG 425	Aronson, Philadelphia	Wassen, 1948	30	P	0
28	BGC B59	Aronson, Philadelphia	Birkhaug, ?	30	P	0
29	BCG 464B	Aronson, Philadelphia	(Japan), 1952	30	P	+
30	BCG 793 Ser2	Aronson, Philadelphia	Van Deinse, 1946	30	P	+
31	BCG 858 Ser2	Aronson, Philadelphia	Van Deinse, 1948	30	P	+
32	BCG 873 Ser2	Aronson, Philadelphia	Van Deinse, 1949	30	P	+
33	BCG 986P	Rosenthal, Chicago	Van Deinse, 1951	14	P, B	+
34	BCG 24, C121	Haaland, Norway	Sievers, 1953	7-14	S, P, PB	0
38	1-BCG Ros.	Vanderviere, McCain	Rosenthal, 1952	?	T	0
39	2-BCG (B) 805	Vanderviere, McCain	Birkhaug, 1952	7	T	0
40	3-BCG (P) 858	Vanderviere, McCain	Aronson, 1951	7	T	0
42	BCG	Bartmann, Berlin	?	30	E	+
47	BCG	Ebina, Japan	Tokyo, 1925	?	B	+
49	BCG	Tracey, Toronto	(Montreal), 1953	30	E	0
50	BCG	Tracey, Toronto	Birkhaug, 1953	30	E	0
14	H37 Rv	Olive View	Steenken, 1950	90	E, T	—
15	H37 Rv	Olive View	Steenken, 1949	90	E, T	—
16	H37 Ra	Olive View	Carpenter, 1949	90	E, T	—
17	H37 Ra	Olive View	Steenken, 1949	90	E, T	—
37	H37 Rv	Tracey, Toronto	(Connaught), 1953	30	E	—
41	4-R1 Rv	Vanderviere, McCain	Steenken, 1952	7	T	—
43	H37 Rv	Bartmann, Berlin	Steenken, 1951	30	E	—
44	H37 Ra	Bartmann, Berlin	Steenken, 1951	30	E	—
45	H37 Rv	Steenken, Trudeau	Baldwin, 1905	?	E	—
46	H37 Ra	Steenken, Trudeau	Baldwin, 1905	?	E	—
48	H37 Rv	Tracey, Toronto	(Connaught), 1953	30	E	—
53	Bovine	Olive View	Corper, 1950	90	E, T	—

*S—Sauton's liquid medium; P—Sauton's potato; B—Bile-potato; E—Egg medium; T—Tween-albumin liquid medium (Dubos)

**+ = used for vaccine production; — = not for vaccine production; 0 = not stated.

1. Egg yolk-glycerol medium—(Corper-Wallenstein[4])
2. Egg potato-glycerol medium—(Loewenstein-Jensen[5])
3. Blood potato-glycerol agar—(Bordet-Gengou[6]), Difco, with 30% whole blood
4. Oleic acid-albumin medium—(Difco-Dubos[7])
5. Tween-albumin liquid medium—(Difco-Dubos[7])

Each culture was labelled with a code number and the authors, in making their observations, did not know the identity of the cultures except by number until the final report was prepared. All cultures, after labelling, were originally streaked on plates of egg-yolk-glycerol medium. After incubation, the plates were observed for colonial types and single colonies of each type were inoculated into Dubos liquid medium. This Dubos medium culture served as the source for all future inoculations.

Each culture was transferred from the fluid medium to the four freshly prepared solid media and to fresh fluid medium and incubated at 37° C. until isolated colonies satisfactory for descriptive purposes were obtained. Most cultures required 14-21 days, though several required 30 or more. Growth was described, photographs prepared and representative cultures chosen for each distinct type of organism recorded.

Five distinct types of organisms were distinguished in the series of 45 cultures. Table II gives a brief description of each type. The BCG cultures showed several forms of colonial appearance which were distinct from each other as well as from other mammalian tubercle bacilli. The most frequently encountered of the BCG types, exemplified by culture number 3, was distinguished by its ability to produce the umbilicated colony described by Mishulow.[8] Though a variety of tubercle bacilli of low or no virulence will produce occasional umbilicated colonies on many solid media, the umbilicate BCG produced this colonial appearance predominantly on both egg and blood media. The development of this form, through its various stages, can be observed in Fig. 1*D*. This colony, after prolonged incubation, was hollow and extremely friable, nearly impossible to emulsify smoothly with the inoculating loop. The low spreading type, less frequently observed, was very similar to these in most respects except that umbilicated colonies were infrequently produced on any medium, particularly on blood agar. Growth had a tendency to be low with rather early flat spreading edges instead of the raised umbilicate colony with its sharply delineated edge (Fig. 1*E*).

Petroff and his co-workers[9] described, in 1929, two types of BCG colonies, an R-form which did not produce disease in guinea pigs and an S-form which did produce disease on intravenous injection. According to their cultural descriptions on egg glycerol medium, R-form colonies corresponded roughly with the umbilicate type, S-form colonies with the low spreading type as observed in these experiments.

On oleic acid-albumin agar, Dubos and his co-workers described a characteristic morphology for strains of BCG.[10] Later, Suter and Dubos[11] described three distinct colonial types from single BCG strains, designating them as spreading, intermediate and non-spreading types. Our own ob-

FIGURE 1A FIGURE 1B FIGURE 1C FIGURE 1D FIGURE 1E

Figure 1: Colonial types of BCG and other acid-fast bacilli on egg yolk-glycerol medium (8 weeks). 1*A*. H37 Rv; 1*B*. H37 Ra; 1*C*. Bovine; 1*D*. Umbilicate BCG, and 1*E*. Spreading BCG.

servations showed that these three types of colonies did exist and that a single colonial type was predominantly associated with a particular strain.

The low spreading type BCG produced primarily an opaque, granular colony on oleic acid albumin agar with edges which occasionally showed a slight flat halo of corded growth. The umbilicate type produced colonies which were flatter, less opaque and were oriented in cords but to a lesser extent than virulent tubercle bacilli with their highly oriented growth. Colonies remained quite small with all strains and the flat granular colonies of the low spreading type showed a tendency to become hollowed with lifted edges after longer incubation. After a short incubation (9-10 days), when colonies are still very small, a predominance of granular, non-oriented growth was present (Fig. 2).

The colonial morphology of the virulent tubercle bacillus, H37 Rv, and its non-pathogenic variant, H37 Ra, the attenuated human strain, R1 Rv, and pathogenic bovine organisms which have been described previously by many workers[12, 13, 1] is shown in Table II.

In Dubos liquid medium, containing Tween 80, all grew fairly rapidly, producing smooth bottom growth without pellicle formation, making it impossible to distinguish grossly among the various types of cultures.

There appeared to be a pattern of resemblance between the cultural morphology of mammalian tubercle bacilli and the nonpathogenic or attenuated variants developed from them. Though sharply distinguishable, H37 Rv and H37 Ra showed a great similarity in color, texture and consistency. The differences were most easily observed on egg yolk-glycerol medium, where the small non-spreading colony of H37 Ra looked much like poorly developed growth of its pathogenic parent strain. Much of the same pattern of development in reverse was seen in the growth of the BCG

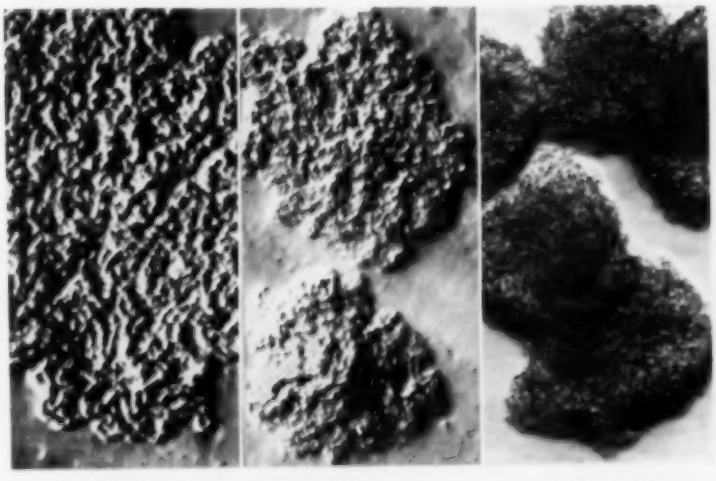

FIGURE 2*A* FIGURE 2*B* FIGURE 2*C*

Figure 2: Colonial types on oleic acid agar at 8 weeks (incident light; x120). 2*A*. H37 Rv (serpentine); 2*B*. BCG (modified serpentine), and 2*C*. H37 Ra (granular).

colony, particularly the umbilicate type, and the initial white domed colony of pathogenic bovine organisms on egg media. The BCG colonies continued to produce their profuse, fragile, rather smooth waxy growth with its distinctive hollow flaky characteristics.

H37 Ra and low spreading type BCG organisms were also similar in their roughness, small colonial size and their tendency to produce granular colonies on oleic acid-albumin agar. One H37 Ra strain, 44, was very difficult to distinguish from the low spreading BCG type. A rough colonial type, isolated from the egg yolk-glycerol plate of 38, was designated 38B, but in all subsequent cultures proved to be indistinguishable from its parent culture, 38, an umbilicate type.

A much higher degree of accuracy in differentiating types of mammalian

TABLE II

COLONIAL CHARACTERISTICS OF MAMMALIAN ACID-FAST BACILLI

	Spreading BCG				Umbilicate BCG				H37 Rv				H37 Ra				Bovine			
CHARACTERS:	*E	L	B	O	E	L	B	O	E	L	B	O	E	L	B	O	E	L	B	O
SHAPE:																				
Round	o	o	o	o	o	o		o	o	o	o	o	o	o	o	o	o	o	o	
Irregular	o	o	o	o					o	o	o	o	o	o			s	s	s	o
Umbilicated	s				o	o	o						s	s						
Morula	s				o	o														
ELEVATION:																				
Flat				o				o				o								o
Slightly raised center	o		o																	
Raised		o			o	o	o		o	o	o		o	o	o	o	o	o	o	
Domed																	o	o	o	
Mammilated									o	o	o									
EDGE:																				
Entire																	o	o	o	
Irregular	o	o		o	o	o	o	o	o	o	o	o	o	o	o	o	s	s	s	
Flat				o				o	o	o	o	o								
Spreading	s								o	o	o	o								o
SURFACE:																				
Smooth						s											o	s		
Granular									o	o	o		o	o		o		o	o	
Nodular		o	o	o	o	o	o		o	o			o	o	o					
Wrinkled	o		o	o				s												
Microscopic:																				
Corded												o								o
Modified corded				s				o												
Non-corded (granular)				o				s								o				
CONSISTENCY:																				
Dry	o	o			o	o			o	o	o	o	o	o	o	o		o	o	o
Moist			o				s										o			
Waxy	o	o	o		o	o	o		o	o	o	o	o	o	o	o	o	o	o	
Granular									o				o	o				o	o	
Flaky					o			o												
Hollow-shell					o	o														
SIZE:																				
Minute-small	s			o	s			o					o	o	o	o				
Medium	o	o			o	o	o		o	o	o	o						o	o	o
Large																				o
GROWTH RATE (days at 37°C.):	14-21				14-21				14				30				21			
COLOR:																				
White			o	o												o	o			o
Cream	o	o			s	o			o	o		o	o	o				o		
Pale buff	s	s						o	s	s	s	s								
Tan			o				o				o								o	
Reddish-brown											s				o					

* E = egg yolk-glycerol medium; L = Loewenstein-Jensen egg-potato-glycerol medium; B = Blood-potato-glycerol medium; O = oleic acid-albumin agar (Dubos)

o = present
s = occasionally present

acid-fast bacilli morphologically may be gained by the use of a series of media rather than reliance upon a single substrate. Two closely related but distinct types of BCG cultures were observed which could be differentiated from pathogenic and non-pathogenic human and pathogenic bovine types of the basis of colonial morphology.

Bacteriophage Susceptibility

The isolation of mycobacteriophages active against tubercle bacilli and the methods employed in these studies have been previously reported.[2] Four phages, labelled D28, D29, D32 and D34, were originally isolated from filtrates of soil samples incubated at 37° C. and periodically enriched with mixtures of saprophytic acid-fast bacilli. Although lytic for a large number of saprophytes, these phages were also observed to lyse a variety of tubercle bacilli during a routine screening of the Olive View stock culture collection of mycobacteria.

The procedure for testing the bacteriophage susceptibility of tubercle bacilli consisted of inoculating a six to eight ounce cotton-plugged bottle containing a basal layer of 30 to 40 ml. of agar with 0.5 to 1 ml. of a turbid culture of tubercle bacilli. Three ml. of melted and cooled semi-solid agar was poured into the bottle, quickly and thoroughly mixed with the inoculum and then placed on a flat surface to solidify. The seeded bottle was incubated until growth was barely visible.

Uniform drops of phage were then deposited on the media with a calibrated platinum-iridium wire loop. The mycobacteriophages employed for testing the susceptibility of tubercle bacilli had been propagated on a stock strain of the tubercle bacillus, H37 Rv, in an attempt to increase the specificity of the phages for the tubercle bacillus. Stock suspensions of mycobacteriophages were prepared by inoculating the surface of a heavily seeded, agar-layered bottle with phage obtained by suspending a portion of a lysed area or plaque in a small quantity of broth. After five to seven days incubation at 37° C., the semi-solid agar layers were carefully harvested, suspended in 5 to 10 ml. of broth, centrifuged and decanted and these supernatant phage suspensions used without filtration. Phage titers of approximately 10^5 to 10^6 particles per ml. were employed in testing for bacteriophage susceptibility.

For the present, no effort was made to quantitate phage susceptibility. Cultures were considered susceptible or resistant on the basis of any observable lysis. The results of a series of tests of phage susceptibility of 36 strains of BCG and a dozen other mammalian tubercle bacilli are summarized in Table III.

All of the stock cultures of human virulent, avirulent and bovine virulent tubercle bacilli tested were highly susceptible to each of the four phages used in this study while none of the BCG cultures tested showed as high and consistent susceptibility (Fig. 3). There were 14 strains of BCG which were lysed at least to some extent by all four phages. Another 14 were lysed by two or three phages producing definite patterns and eight strains were not classified because of inconsistencies or lack of uniformity

of results. Thus, 28 of 36 BCG strains tested could be divided into definite groups according to their phage susceptibility. No BCG strain tested was consistently resistant to all phages.

Variations in the reproducibility of patterns of susceptibility were noted with phages D28, D32 and D34. These were ascribed to the variations in the titer of activity of the particular phage preparations or to variations in technics employed in these investigations. However, two cultures of H37 Rv, previously observed to be susceptible to all four phages were similarly lysed by all the preparations used.

Although various cultures of H37 Ra and H37 Rv obtained from various sources showed a uniform pattern of susceptibility, strains of BCG exhibited differences in their lytic patterns. These patterns, moreover, did not correspond entirely to the history of the source or to the cultural morphology of the strains tested.

Animal Inoculation Experiments

All organisms used in the study were tested for antigenicity and pathogenicity and the BCG strains for immunogenicity in guinea pigs. Two tuberculin-negative guinea pigs were inoculated subcutaneously with 1 ml.

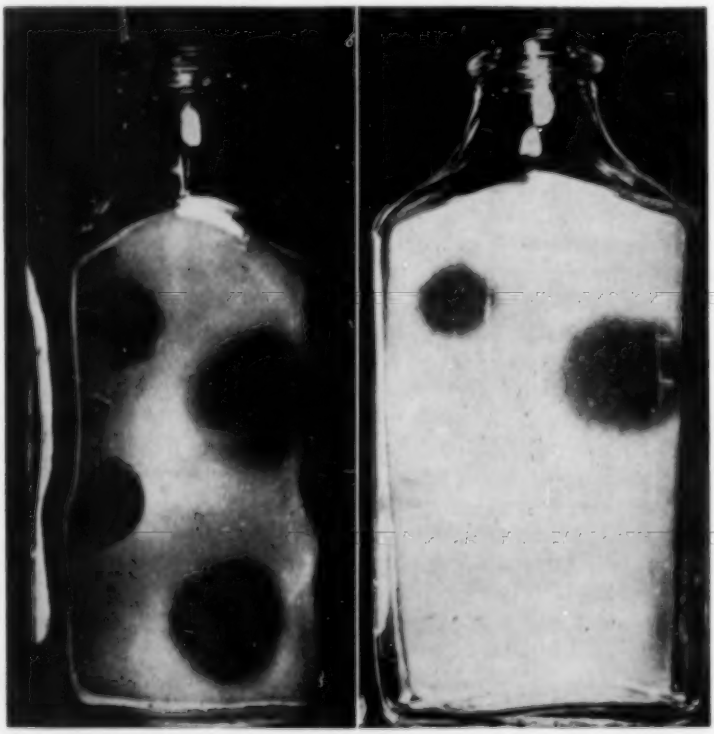

FIGURE 3*A* FIGURE 3*B*

Figure 3: Bacteriophage lysis of BCG and virulent bovine tubercle bacilli. 3*A*. Virulent bovine (Corper) and 3*B*. BCG No. 39.

of a saline suspension of actively-growing bacilli. The suspensions were diluted so that one pig received 1 mg. of organisms, the other 0.001 mg. per ml. Tuberculin tests were performed on all animals at seven weeks and nine weeks. At the ninth week, all animals who had received BCG strains were challenged with 1 ml. of a suspension of an H37 Rv strain which contained 0.001 mg. per ml. Four tuberculin-negative guinea pigs were also injected with this same suspension to serve as controls.

TABLE III

BACTERIOPHAGE SUSCEPTIBILITY PATTERNS OF 48 STRAINS OF MAMMALIAN TUBERCLE BACILLI

Phage Pattern D28	D29	D32	D34	BCG	H37 Rv	H37 Ra	R1 Rv	Bovine Virulent	Total
+	+	+	+	1, 2, 3, 4, 5, 19, 26, 29, 31, 33, 34 36, 40, 50	14, 15, 37, 43, 45, 48	16, 17, 44, 46	41	53	26
+	+	+	—	6, 18					2
+	+	—	+	11, 12, 13, 30, 39, 49					6
+	+	—	—	8, 10, 27, 28, 32, 37					6
Unclassified				9, 21, 23, 24, 25, 38, 38B, 42					8
Total				36	6	4	1	1	48

Four weeks after challenge with the virulent bacillus, one of the controls was found to have tuberculous lesions in the inguinal nodes, spleen and liver. Eight weeks after the challenge dose, or 17 weeks from the initial injection of the test strains, all animals, including the controls, were tuberculin tested, then sacrificed. At autopsy, the site of inoculation was inspected and the organs were then examined macroscopically and graded according to the classification long in use at Olive View as published in 1932.

As shown in Table IV, all strains used produced levels of response to tuberculin ranging from one to three plus reactions. Several BCG strains and one H37 Ra strain produced as high a level of response to tuberculin as most of the H37 Rv cultures. Local lesions at the site of inoculation developed as varying amounts of induration or nodules about two weeks after infection with BCG which did not break down or ulcerate as did the sites of inoculation in animals receiving H37 Rv. The regional lymph nodes enlarged palpably and sometimes visibly and softened similar to those with H37 Rv. Later, the nodes tended to decrease in size and become absorbed, in some cases apparently completely disappeared grossly, while in others inspissated caseous contents remained.

At autopsy, the control animals injected with the challenge dose of H37 Rv showed a large amount of progressive disease present. The animals injected with five strains (4, 8, 27, 30, 31) showed no evidence of progressive disease and all other animals which had received BCG strains showed some evidence of infection but, in all cases, much below the level of the control animals which had received only the virulent challenge dose.

There was no evidence that either type of BCG differed in their antigenicity and immunogenicity. Since all animals injected with BCG in these studies received a challenge dose of a strongly virulent organism, this particular experiment did not reveal the presence of any disease produced by BCG alone but only disease caused by the superimposed H37 Rv.

Cytologic and Cytochemical Virulence Tests

Middlebrook and Dubos[14] introduced the neutral red test in 1948 as a simple *in vitro* method of differentiating mammalian tubercle bacilli on the basis of their virulence. Highly pathogenic organisms such as H37 Rv produced long serpentine cords in culture and fixed neutral red in a highly alkaline medium. Organisms, such as H37 Ra, which were not disease-producing, did not form cords, showed no orientation and did not fix neutral red to any observable extent. Attenuated mammalian bacilli gave intermediate degrees of orientation and neutral red fixation, suggesting their incapability of producing progressive disease in animals.

Neutral red determinations were performed by the original Middlebrook and Dubos technic, involving two treatment with 50 per cent methanol of cells at 37° C. for 60 minutes each time followed by resuspension in alka-

TABLE IV

BCG CULTURES

Morphologic Types	Antigenicity	Immunogenicity	Neutral Red	Cording	Phage Susceptibility D28	D29	D32	D34	Cultures (Code No.)
Umbilicate BCG			+	+	+	+	—	+	11
	++	sl	+	+	+	+	—	—	47
	+++	sl	±	+	+	+	—	—	28
	++	sl	—	+	Unclassified				1, 25
	++	sl	—	+	+	+	+	+	2, 33, 50, 36
		sl	+	—	+	+	+	—	18
	++	+	—	—	+	+	—	+	30
Low Spreading BCG	++	sl	++	+	+	+	+	—	6
	++	sl	+	+	+	+	+	+	3, 19, 26
	+++		+	+	+	+	—	+	12, 13, 39, 49
	+	+	±	+	+	+	+	+	4, 31
	+++	sl	—	sl	+	+	+	+	5, 34, 40
	++	sl	±	+	Unclassified				9, 23, 24, 38B, 42
	++	sl	—	+	+	+	—	—	32
	++	sl	—	sl	Unclassified				38
	++	+	—	sl	+	+	—	—	8, 10, 27
Human virulent type	+++	sl	++	—	+	+	+	+	29

OTHER TUBERCLE BACILLI

	Virulence								
Human virulent type	+++	+	++++	++	+	+	+	+	14, 15, 37, 43, 45
	++		++	Variable	+	+	+	+	48
	++	—	—	sl	+	+	+	+	41
Human avirulent type	++	sl	±	—	+	+	+	+	16
	±	—	—	sl	+	+	+	+	44, 46
	+++	—	—	—	+	+	+	+	17
Bovine virulent type			++++	++	+	+	+	+	53

line buffer solution and the final addition of neutral red. This method was used to test cells scraped from solid egg yolk-glycerol medium as well as on centrifuged sediments from Dubos Tween-albumin medium. The test was considered positive if the granular masses of organisms showed any pinkish-red coloration, negative if there was no sign of red color.

Cording was observed by preparing thin wet preparations from the concentrated growth in Dubos medium and visualizing this largely undisturbed growth by phase-contrast microscopy. The bright medium phase-contrast oil immersion objective (Spencer) was used and all cultures were checked at 17-21 days.

Results of the neutral red tests are summarized in Table IV. In some cases the cell sediment from Dubos medium was negative while the scraped growth from egg yolk-glycerol medium appeared to be moderately to strongly positive. By both technics, all cultures of human and bovine tubercle bacilli which produced progressive disease in animals gave consistently strong positive neutral red tests and showed evidence of intense cording with parallel cell orientation. The strains of BCG showed variations both in neutral red reactions and in the degree of cording observed. A strongly antigenic strain, 29, with low immunogenicity, showed moderately positive neutral red absorption and no evidence of cording. R1 Rv, a culture which was not pathogenic for guinea pigs, showed only slight cording and negative neutral red tests on repeated examination. Two strains of the avirulent human variant, H37 Ra, revealed negative neutral red and cording tests; a third culture showed no cording and negative neutral red tests with the growth sediment from fluid media but gave repeated positive neutral red tests with growth from solid media. The significance of this finding could not be assessed.

The phase-contrast observations, in addition, revealed evidence of pleomorphism in BCG strains previously described.[1] While true human virulent and avirulent and bovine virulent bacilli showed long, usually straight slender rods with dense polar granules, BCG showed a much higher degree of variation, with swollen forms, clubs and other aberrations and multiple dense granulations. This cellular morphologic variation was much more characteristic of the umbilicate type than the low spreading type. The latter were usually more slender, showed less granularity and had much less tendency to produce swellings and other unusual forms.

Fixed films of these 17-21 day growths in fluid media were stained by the Ziehl-Neelsen technic and with Giemsa stain to determine the purity of the cultures and their morphologic character. Stained films revealed all cultures to be strongly acid-fast at 17-21 days and the Giemsa-stained preparations confirmed the cellular observations described by phase-contrast microscopy.

Results and Discussion

Table IV illustrates the wide variety of patterns obtained when all the cultures studied were grouped according to their morphologic types and the results of other technics tabulated. Twenty-four BCG strains fell into the umbilicated type, 11 were of the low spreading type and a third

single culture, 29, produced growth difficult to distinguish from a virulent mammalian tubercle bacillus. Generally, most BCG cultures showed some evidence of cording and more than half were neutral red positive, the reactions varying from weak to moderately strong. BCG strain 29 proved unusual also in the fact that cording was not observed on repeated occasions though the neutral red test was moderately positive and the culture possessed both high antigenicity and a virulent growth type. Attempts to correlate the various characteristics of the BCG strains with their sources, phage types, or morhology revealed no distinct overall trends of any variety. It appeared that the 36 BCG cultures produced an array of patterns by the bacteriologic technics employed; they revealed, in common, however, the ability to produce dermal sensitivity to tuberculin and to stimulate distinct immunogenic response to challenge with virulent tubercle bacilli. The level of both antigenic and immunogenic response could not be correlated with the other characteristics studied.

The virulent and avirulent human bacilli showed much less variation. Their morphologic types were distinct in character, all belonged to the same phage susceptibility group. The virulent organisms produced strong neutral red reactions and evidence of cording; the avirulent cultures showed either no cording and negative neutral red reactions or equivocal evidence of one or the other. In regard to these two characteristics, it appeared proper to conclude that cultures showing a high degree of cording and strongly positive neutral red reactions were apt to produce progressive tuberculous disease and that cultures exhibiting neither character did not produce disease. The level of these two characteristics did not appear to be correlated with the antigenicity of all the strains tested nor to the immunogenicity of the BCG strains studied.

All the cultures had been originally grown for many generations on both potato and Sauton's liquid medium. More than half, when received, had been maintained on Egg or Tween-albumin media for some time and were thus carried during this series of experiments. More than half the umbilicate or R types had been maintained on egg or Tween-albumin media for long periods and more than half of the S or low spreading types had been subcultured regularly on potato or Sauton's medium.

The repeated previous transfers on egg medium of nearly half the cultures may have accentuated "dissociation," or as it is now usually viewed, mutations may have been preserved which would have been suppressed in growth on the standard Sauton's potato medium. The fact that variant forms were more common in the cultures which had been so maintained supports this view. Since all these cultures were picked from single colonies on egg media would increase the frequency with which they would be noted. BCG properly perpetuated according to directions may accordingly show less variations than appear here but scarcely precludes them. It is apparent that the potentiality for such variations still exist. Whether morphologic appearance, physio-chemical tests and phage susceptibility variations indicates concomitant alterations in immunogenic and pathogenic properties requires further investigation.

SUMMARY

Cultural and biochemical characteristics, bacteriophage susceptibility, antigenicity and immunogenicity of 36 strains of BCG obtained from many different sources were studied to determine the extent of their variation.

Some BCG cultures on various egg media, oleic acid-albumin agar or blood agar showed an umbilicated type of colony, but others a low spreading type. The extent of cording and the intensity of neutral red staining varied in the different strains but was always less than with virulent tubercle bacilli. Some BCG cultures were susceptible only to two of the four phage preparations used but some were also lysed to some extent by the others, though none as completely as the virulent tubercle bacilli.

The differences in microscopic and macroscopic morphology, cytochemical characteristics and susceptibility to four recently-isolated bacteriophages among these strains emphasizes the extent of the variations which may occur in cultures of BCG.

RESUMEN

Se estudian los caracteres de cultivos, bioquímicos, susceptibilidad al bacteriófago, antigenicidad e inmunogenidad, de 36 cepas de BCG obtenidos de múltiples fuentes diferentes, con el fin de determinar las variaciones.

Algunos cultivos de BCG sobre various medios de huevo, agar ácido oleico-albúmina o sangre agar, mostraron un tipo umbilicado de colonia pero otros un tipo diseminado.

Las extensión del alineamiento y la intensidad de la coloración con el rojo neutro varió con las cepas, pero fué menos esavariación que con el bacilo de la tuberculosis virulento.

Algunos cultivos de BCG fueron susceptibles sólo a dos de las cuatro preparaciones de fagos usadas, pero algunas fueron lisadas también en cierta medida por los otros fagos, aunque ninguna tan completamente como el bacilo virulento.

Las diferencias en la morfología microscópica y macroscópica, las características cito-químicas y la susceptibilidad a cuatro bacteriófagos recientemente aislados entre estas cepas realza la extensión de las variaciones que pueden ocurrir en los cultivos de BCG.

RESUME

Les auteurs ont étudié les caractères de culture et les propriétés biochimiques, la sensibilité au bactériophage, le pouvoir antigénique et immunogène de 36 souches de B.C.G. provenant de différentes sources afin de déterminer l'importance de leurs variations.

Quelques cultures de B.C.G. à partir de différents milieur des oeufs, à l'agar acide oléique albumineux ou à l'agar sanguin, donnèrent un type de colonie ombiliquée mais d'autres révélèrent un type faiblement étendu. La disposition en corde et l'intensité de la coloration au rouge neutre varièrent selon les différentes souches, mais furent toujours moindres que lorsqu'il s'agit de bacilles tuberculeux virulents. Quelques cultures de B.C.G. ne furent sensibles qu'à deux des quatre préparations inhibitrices utilisées, mais quelques-unes furent aussi "lysées" à un certain degré par les autres,

bien qu'aucune ne l'ait été aussi complètement que le bacille tuberculeux virulent.

Les différences morphologiques étudiées microscopiquement et macroscopiquement, les caractéristiques cytochimiques et la sensiibilité à quatre bactériophages récemment isolés parmi ces souches, montrent d'une façon frappante l'étendue des variations qui peuvent survenir dans les cultures de B.C.G.

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The Influence of Chemo-antibiotic Treatment on Tubercle Bacilli (Culture Properties and Guinea pig Pathogenicity)

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The advent of chemo-antibiotic agents has brought about a revolution in the treatment of tuberculosis. Prolonged bed-rest is, of course, a form of treatment that cannot be dispensed with. But measures such as artificial pneumothorax and pneumoperitoneum have become decidedly less common than before. Previously inoperable cases of tuberculosis may now be made fit for operative therapy. Tuberculous processes are also brought under better control with chemo-antibiotic therapy. Recovery is more rapid, more certain and more definite.

The new method of treatment has also made tubercle bacilli themselves a matter of interest. Their reactions to the influence of chemo-antibiotic agents have been studied—and are still studied—with lively interest. Although many problems remain unsolved, important progress has been made. The usual agents, streptomycin, para-aminosalicylic acid (PAS) and isoniazid (INH) have mainly a bacteriostatic action, but in certain concentrations they may be bacteriocidal or even bacteriolytic. It is evident that they have different modes of action since tubercle bacilli resistant to one agent may be highly sensitive to the others. INH seems to be in a category of its own. By virtue of its smaller molecular size it can more readily than the other agents penetrate into the tissues. It is therefore active intracellularly, passes easily into the cerebrospinal fluid, and may be shown in high concentration in the pleural cavity already two and one half hours after administration. Radioactive labelled INH has been encountered in caseous tissue (in lungs and lymph nodes) in high concentration after three to five hours. While streptomycin inhibits bacterial proliferation immediately, INH acts only after a latency during which the bacterial population is almost doubled. This "delayed" bacteriostasis is reminiscent of the action of sulphonamides on the organisms that are sensitive to these agents.

The occurrence of primary and secondary resistance to the new antituberculous agents has been a matter of eager research. The literature on this subject is profuse. But it has only recently been observed that tubercle bacilli from persons treated with chemo-antibiotics agents are not infrequently difficult to culture, and may lack their characteristic pathogenicity to guinea pigs.

In examination of resected tissues from lungs, Medlar, Bernstein and Steward[1] (1952) found that 73 per cent of the specimens contained acid-fast bacilli, although merely 20 per cent gave positive cultures of tubercle bacilli. In a few cases guinea pigs were inoculated with an abundance of tubercle bacilli without the development of tuberculous lesions. The

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authors therefore debate whether the organisms were dead or alive, but do not arrive at any finality on this point. Beck and Yegian[2] who also examined resected specimens demonstrated acid-fast bacilli in 16 out of 17 patients treated with chemo-antibiotics before operation, but they were able to culture them in only four cases. In two out of eight patients treated repeatedly with such agents bacilli occurred which, moreover, were neither culturable nor pathogenic to guinea pigs. In view of the fact that similar results may occasionally be obtained from untreated patients, the authors believed that it was difficult to determine to what extent this was attributable to chemo-antibiotic treatment and to the natural resistance of the host. Steenken and Wolinsky[3] (1953) found that bacilli from patients treated with isoniazid could become non-pathogenic to guinea pigs. This was independent of the duration of treatment and the degree of resistance to the agent. The authors warn against the misconception that such modified bacilli are harmless to the patient and his environment. They can undoubtedly still give rise to serious exacerbations of the disease. Bader[4] (1954) recently explained the negative cultures and animal inoculations as being a result of injury to the bacilli, primarily through the chemo-antibiotic agent administered, and secondarily through the treatment of the sputum with sulphuric acid before culture or inoculation. The significance of the latter had somewhat earlier been shown by Silveira.[5] Sweany and Perez[6] also state that tubercle bacilli from patients treated with chemo-antibiotic agents may lose their capacity for producing tuberculosis in guinea pigs.

I have occasionally obtained negative cultures despite the occurrence of acid-fast bacilli in the sputum. In certain cases saprophytes have undoubtedly been involved (Hedvall[7]), but in other cases the tubercle bacilli were dead or—as a result of sulphuric acid preparation—injured with reduced power of growth on culture media. I was not aware of any increased occurrence of such cases during the time that streptomycin, alone or in combination with PAS, was in use at this clinic. Such has been the experience, however, after the addition of INH to the array of medicinal agents. Four cases are briefly reported.

It will be necessary first to make certain explanations pertaining to the tables accompanying the cases. These have been carried up to June 9, 1954, when the material was reviewed. In *direct microscopic examination*, "+" denotes the occurrence of 1-3 acid-fast bacilli on the entire smear. "++" signifies a somewhat more plentiful occurrence of bacilli but not to the extent that they are encountered in every field. "+++" indicates that 1-3 bacilli are found in each field, "++++" that bacilli are abundant in each field, and "++++++" means that the bacilli form as it were a red mat (with Ziehl-Neelsen stain). In *cultures* "+" denotes the occurrence of solitary tuberculous colonies in the three tubes. "++" signifies a fairly plentiful occurrence of colonies, "+++" indicates an abundance of colonies, "++++" means that the colonies to a large extent coalesce and "++++++" that all three tubes are quite overgrown with tubercle bacilli. "Pos," finally, denotes that growth of tubercle bacilli was obtained and used for resistance determinations, but since the extent of growth was not noted down by the one who made the tests, this could not be represented in any other way in the table. The cultures were assessed definitely at six weeks. Both for cultures and for guinea pig inoculation the material was first treated with 9.25 per cent sulphuric acid.

The tables below indicate the duration of hospital care and the chemo-antibiotic agents used, as well as the relevant times. Streptomycin was usually given in a dose of 0.5 g. daily for three months (continuous line) followed by 0.5 g. every fifth day for a variable period (interrupted line). In certain cases where it was necessary,

and where the bacilli were sensitive to the agent, the course of treatment was repeated. This also applies to INH and PAS. INH was given in a dose of 4 mg. per kilogram body weight and PAS in a dose of 3 g. 4 times daily.

Case 1: G. B., born Feb. 2, 1924. Designer. Right sided pulmonary tuberculosis diagnosed in May 1944. Artificial pneumothorax induced at once. Treated at the University Lung Clinic in Uppsala from September 1944 to March 1945. A cavity at the right apex was present on admission. After cautery of adhesions the lung collapsed satisfactorily and the cavity disappeared. In January 1946 the process had spread to the left lung, and the patient had to be readmitted (January to April 1946). Left sided artificial pneumothorax was now induced and maintained ambulantly. Pneumothorax treatment was discontinued on the right side in March 1950 and on the left side in May 1952. The lungs then re-expanded normally. In November 1952 he had hemoptysis. An exudative process was diagnosed at the right apex with some small cavities. Again admitted to the University Lung Clinic in December 1952 to July 1953. He now received chemo-antibiotic treatment for the first time. The condition improved somewhat but already in November the same year he had hemoptysis again. The exudative process had increased. He was readmitted for sanatorium care and again received chemo-antibiotic treatment, but it was only after right sided thoracoplasty in February 1954 that the condition really improved, and the patient became free from bacilli (Figs. 1 and 2).

Case 1, therefore, is a patient who had previously received prolonged bilateral artificial pneumothorax treatment for pulmonary tuberculosis. The lesions had recurred on the right side about two and one half years after discontinuation of artificial pneumothorax. Chemo-antibiotic treatment halted the progress of the disease only temporarily. It was only after right sided thoracoplasty in February 1954 that any real improvement occurred. On the occasion when resistance was determined the tubercle bacilli proved to be very sensitive to streptomycin, INH and PAS. He was, moreover, treated with these agents (Table I). On December 15, 1953, when he had received streptomycin and INH for a long time, (streptomycin 76.5 g. and INH 38.15 g.) but PAS only for a short period (PAS 396 g.), both culture and guinea pig inoculation gave negative results despite the occurrence of tubercle bacilli (++) in sputum smears. The same thing occurred on February 10, 1954. Smear examinations, guinea pig inocula-

FIGURE 1

FIGURE 2

Figure 1.—Case 1: Born Feb. 2, 1924. Previously received prolonged bilateral artificial pneumothorax treatment for pulmonary tuberculosis. Fresh lesion with small cavities at the right apex in November 1952. Prolonged chemo-antibiotic treatment resulted in only a moderate improvement.

Figure 2.—Case 1: After right sided thoracoplasty in February 1954 the condition is definitely improved, and the patient is free from tubercle bacilli.

TABLE I

Case 1. G.B. born Feb. 2, 1924.

Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum		
1952	Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation
12/19	++			3/14	—			7/18		+		1/14	—			4/10	—		
12/20	++			3/21	—			11/12	—			1/6	—			4/14	—		
12/21	+++			4/1	—			11/13	—			1/20	—			4/22	—	—	
12/23	++			4/11	—			11/14	++++			1/23	—			4/23	—	—	
12/24	—			4/15	—			11/16	++++			1/27	—			4/24	—		
12/29	+			4/18	—			11/18	—			2/3	++			4/26	—	+[1]	
1953				4/22	—			11/21	++			2/6	++			4/29	—	—	—
1/9	—			5/6	—			11/25	—			2/10	++	—	—	4/30	—	—	—
1/10		+++		5/9	—			11/28	—			2/17	—			5/3	—	—	—
1/14	—			5/16	—			12/5	++			3/24	—			5/5	—	—	—
1/24	—			5/20	—			12/15	++	—	—	3/26	—	—		5/6	—	—	
1/31	—			6/3	—			12/31	++			3/27	—	—		5/8	—		
2/3	—			6/6	—			*1954*				3/30	—	—		5/15	—		
2/7	—			6/13	—			1/2	++			4/3	—			5/25	—		
2/25		+		6/26		—		1/9	—			4/7	—			6/5	—		

[1]=1 colony

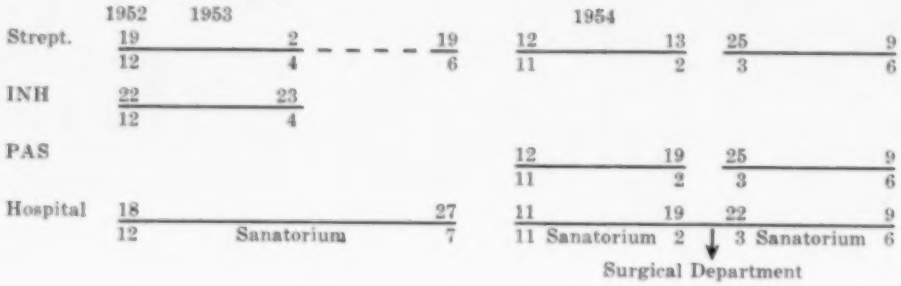


FIGURE 3

FIGURE 4

FIGURE 5

Figure 3.—Case 2: born Nov. 25, 1901. On admission in June 1953 extensive tuberculous lesions in at least two-thirds of the right lung and the middle field of the left lung. Large system of cavities in the right upper lobe. Abundant tubercle bacilli in the sputum. Poor general condition, cachectic, highly febrile.

Figure 4.—Case 2: With chemotherapy the lesions were improved. It was thus possible to perform thoracoplasty.

Figure 5.—Case 2: Condition after rightsided thoracoplasty in March 1954. Gradual further improvement and freedom from bacilli.

tions and cultures have since then been negative, with the exception of a culture which was positive April 26 (only one colony). He had received, on June 9, 1954, altogether 134.5 g. streptomycin, 38.15 g. INH and 2100 g. PAS.

Case 2. G. A., born November 25, 1901. Bilateral exudative pulmonary tuberculosis diagnosed in June 1953. The lesions were extensive, affecting fully two-thirds of the right lung and the middle field of the left lung. At the apex of the right was a large system of cavities. The general condition was poor. He was cachectic and highly febrile. Admitted to the University Lung Clinic in Uppsala on July 1, 1953. Pneumoperitoneum attempted August 10, 1953 to February 5, 1954, and rightsided pneumothorax September 21, 1953 to January 31, 1954. These procedures were evidently of little avail. The apex was adherent and the cavities did not collapse. Chemo-antibiotic treatment, on the other hand, played an important part in this case. The exudative lesions receded, the temperature fell and the general condition improved steadily. Finally it was possible, in March 1954, to collapse the lung with rightsided thoracoplasty. The condition is now surprisingly good. The sputum no longer contains tubercle bacilli (Figs. 3-5).

Case 2 thus started with advanced, exudative bilateral pulmonary tuberculosis with large cavities at the right apex. Pneumoperitoneum and pneumothorax did not contribute materially to the improvement. But with chemo-antibiotic therapy it was possible to make the patient fit for right sided thoracoplasty. The tubercle bacilli when tested for resistance, the last time December 19, 1953, proved to be sensitive to streptomycin, INH and PAS, the agents with which he was treated. Table II shows that on July 7, 1953 both culture and guinea pig inoculation were negative despite an abundance of tubercle bacilli (+++++) in the sputum. It should be pointed out that chemo-antibiotic treatment had been given only for one week, so that it is doubtful whether this treatment could be responsible. Later on (between July 15 and October 10, 1953) tubercle bacilli were cultured on five occasions for resistance determinations. Between October 14 and 28, however, three cultures and two guinea pig inoculations were negative despite the presence of tubercle bacilli in the sputum. The bacilli have also subsequently been cultured, but only with the growth of isolated colonies of tubercle bacilli. Until October 14, he had received 49.5 g. streptomycin, 19.18 g. INH and 1272 g. PAS. Altogether until June 9, 1954 he has received 72.5 g. streptomycin, 28.65 g. INH and 2340 g. PAS.

Case 3. R. P., born February 5, 1923. Turner. Right sided pulmonary tuberculosis diagnosed in January 1946. He had been admitted on repeated occasions to the University Lung Clinic in Uppsala on account of recurrences. Right sided pneumothorax induced in April 1947. The process spread to the left apex in January 1951. In June the same year a cavity developed in the still pneumothorax-treated right lung. Increased refillings and chemo-antibiotic treatment failed to bring about collapse of the cavity. The lung was therefore allowed to re-expand. In August right sided thoracoplasty was performed instead. No tubercle bacilli could be shown in the sputum just before and after this operation. In October the lesions at the left apex progressed, and eventually a cavity developed there. At the same time an abundance of tubercle bacilli appeared in the sputum. When left sided artificial pneumothorax was induced the cavity collapsed, the general condition improved steadily and the bacilli again disappeared from the sputum (Figs. 6-8).

Case 3 was admitted repeatedly to sanatorium on account of stubborn recurrences. Right sided artificial pneumothorax did not bring about a cure. Right sided thoracoplasty had to be performed later. After this, older lesions at the left apex progressed, a cavity developed, and bacilli again appeared in the sputum. These had earlier been culturable. Now (December 1953) they gave either completely negative cultures and guinea pig inoculations, on repeated examinations, or else they gave rise to only isolated colonies although abundant tubercle bacilli (up to ++++)

FIGURE 6 FIGURE 7 FIGURE 8

Figure 6.—Case 3: Born Feb. 5, 1923. Bilateral pulmonary tuberculosis where a large cavity developed in the right lung under pneumothorax treatment. Since the cavity could not be made to collapse the lung was allowed to re-expand in preparation for thoracoplasty.

Figure 7.—Case 3: Right sided thoracoplasty performed in August 1953. The patient then became free from bacilli. The left sided lesions which had been suppressed by chemotherapy have now exacerbated and given rise to a cavity. Tubercle bacilli again present. This time chemotherapy brought about no improvement.

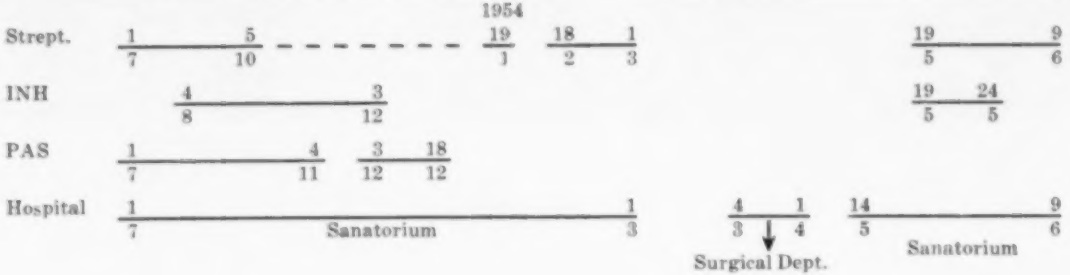
Figure 8.—Case 3: Left sided artificial pneumothorax has been induced and the condition is satisfactory. The patient is free from bacilli.

could be seen by microscopic examination of the sputum. These few colonies show no correspondence with the numbers of tubercle bacilli in the material inoculated onto the culture medium; the reluctance of these bacilli to be cultured is therefore unquestionable. They were sensitive to

TABLE II

Case 2. G.A. born Nov. 25, 1901.

Date 1953	T.B. in Sputum: Direct Examination	Culture	Guinea pig Inoculation	Date	T.B. in Sputum: Direct Examination	Culture	Guinea pig Inoculation	Date	T.B. in Sputum: Direct Examination	Culture	Guinea pig Inoculation	Date	T.B. in Sputum: Direct Examination	Culture	Guinea pig Inoculation	Date	T.B. in Sputum: Direct Examination	Culture	Guinea pig Inoculation
7/2	+++++			8/19	+++			10/24	+	—		1/16	—			3/31	—		
7/3	+++++			8/22	++			10/28	++	—	—	1/23	—	—		4/10	++	+	
7/4	+++++			8/26	++			11/4	+			1/27	—			5/15	—	—	
7/7	+++++	—	—	8/29	++			11/11	—	—		1/30	—			5/19	—	—	
7/11	+++++			9/2	+++			11/18	—			2/3	++			5/20	—	—	
7/15	+++	pos.		9/5	+++			11/25	—			2/6	++			5/21	—	—	
7/18	++++			9/9	++			11/28	+			2/9	—			5/22	—		
7/22	+++			9/12	++	pos.		12/3	—	—		2/10	++	+	—	5/24	—		
7/25	+++			9/16	++			12/5	—			2/11	++	pos.		5/25	—		
7/29	+++			9/19	++			12/9	—			2/13	++			5/26	—		
8/5	++++			9/23	++			12/12	—			2/17	++			5/28	—		
8/8	++	pos.		9/26	++	pos.		12/15	—	—		2/20	++			5/29	—		
8/11	++			9/30	+			12/16	—			2/24	++			5/31	—		
8/12	++			3/10	—			12/19	++	pos.		2/27	++			6/1	—		
8/13	+++			10/7	++	pos.		12/23	+			3/6	++			6/2	—		
8/14	+++			10/10	+			*1954*				3/10	—			6/4	—		
8/15	+++			10/14	++	—	—	1/2	+			3/13	++	+		6/5	—		
8/17	++			10/17	+			1/8	—			3/17	—			6/9	—		
8/18	++++			10/21	—			1/13	+			3/24	+						



streptomycin, INH and PAS when tested. At the latest determination (March 18, 1954), however, values were obtained which indicated that the bacilli were resistant to PAS. It is possible that this value is erroneous, as will be pointed out elsewhere. Until December 7, 1953, when the bacilli became difficult to culture and gave negative guinea pig tests, the patient had received 104 g. streptomycin, 34.125 g. INH and 2320 g. PAS. Up to June 9, 1954 he had received altogether 156 g. streptomycin, 52.125 g. INH and 2320 g. PAS.

Case 4. S. N., born Aug. 3, 1902. Blacksmith. Left sided pulmonary tuberculosis was diagnosed in January 1954 and he was admitted to the University Lung Clinic in Uppsala, where he is still under treatment. There was a fairly large, irregular cavity at the left apex. Surrounding this and extending down to the level of the hilum a patchy, parenchymatous opacity could be observed. Later on the upper lobe became atelectatic. Abundant tubercle bacilli could be shown in the sputum. Bronchoscopy, however, revealed no bronchial lesions. The atelectasis gradually regressed and the lung re-expanded. Some of the lesions disappeared with chemotherapy and bed-rest, but the cavity persists. Although the bacilli in the sputum have decreased, thoracoplasty will probably become necessary (Figs. 9-10).

Case 4 showed lesions localized mainly to the left upper lobe with a cavity apically. After a period of upper lobe atelectasis the lung re-expanded. The condition improved, but a cavity persists. Thoracoplasty remains to be done. From Table IV it will be seen that the sputum has usually contained an abundance of tubercle bacilli. Positive guinea pig inoculations were obtained from sputum on February 23, April 7 and 8, 1954. Two more guinea pig tests in February were positive but as no date was supplied they could not be included in the table. From April 9 (even more strikingly from April 26) repeated cultures and guinea pig tests were negative despite the occurrence of tubercle bacilli in the sputum (++ in direct microscopic examination). The bacilli proved to be sensitive to streptomycin, INH and PAS. Until April 9, 1954, he had received 40.5 g. streptomycin, 11.875 g. INH and 394 g. PAS. Up to June 9, 1954, he had received altogether 50.5 g. streptomycin, 28.38 g. INH and 394 g. PAS.

FIGURE 9

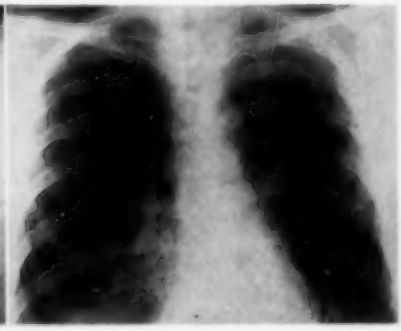


FIGURE 10

Figure 9.—Case 4: Born Aug. 3, 1902. Advanced lesions in the left lung—A fairly large cavity at the apex. Abundant tubercle bacilli in the sputum.

Figure 10.—Case 4: With chemotherapy the lesions have largely been healed but a cavity persists at the apex. Bacilli present occasionally. Thoracoplasty will probably become necessary.

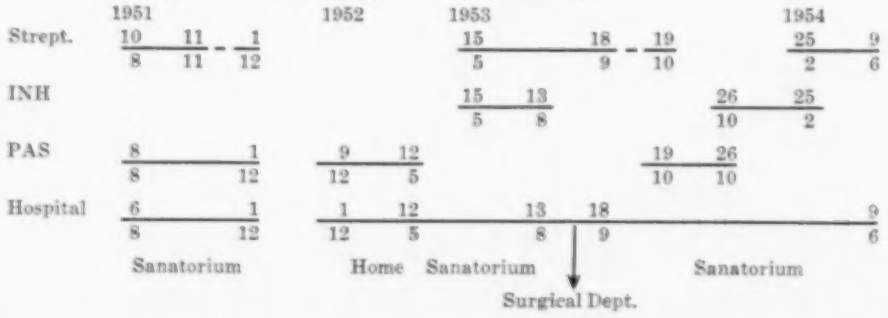
TABLE III

Case 3. R.P. born Feb. 5, 1923.

Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum		
1951	Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation
8/7	—			11/17	—			8/5	—			12/16	—			3/15	++	—	
8/8	+			11/21	—			8/8	—			12/19	+++			3/16	+++	—	
8/15	++			11/24	—			8/12	—			12/22	+++			3/17	—	—	
8/18	+++			11/28	—			9/19	—			12/30	++++	—	—	3/18	—	+[2]	
8/22	—			*1953*				9/21	—			*1954*				3/19	+	—	
8/29	—			5/13	++++			9/22	—			1/2	++++			3/20	—	—	—
9/1	++			5/15	++++	pos.		9/23	—			1/9	+++		—	3/22	—	—	
9/3	—			5/16	+++			9/26	—			1/13	++++			3/23	—	—	
9/4	—			5/20	+++			9/30	—			1/16	++			3/24	—	—	
9/5	—			5/23	++			10/3	—			1/20	—			3/25	—	—	
9/6	—			5/27	—			10/7	—			1/23	+++			3/26	—	+[1]	
9/7	++			5/30	++			10/10	—	—		1/25	++	—	—	3/27	++		
9/8	++			6/3	—			10/13	—			1/27	++++			3/29	+	—	—
9/12	—			6/6	++			10/17	—			1/30	+++			3/30	—		
9/15	++			6/10	+			10/21	++	+		2/3	++			4/1	—		
9/19	—			6/13	—			10/24	—			2/6	++			4/2	—		
9/22	—			6/17	+	+		10/28	+	pos.		2/9	++			4/3	—		

9/26	—		6/24	+		11/4	++			2/10	++		—	—	4/5	—			
9/29	—		6/27	—		11/7	+++			2/17	++++		+	—	4/7	—			
10/10	—		7/1	—		11/14	+++			2/20	++++				4/8	—			
10/13	++		7/4	—		11/18	—			2/24	++++				4/9	+			
10/17	—		7/8	—		11/21	+			2/27	++++				4/10	—			
10/24	—		7/11	—		11/25	—			3/3	++		—		4/12	—			
10/27	—		7/15	—		11/28	—			3/6	++		+[1]		4/13	—			
10/31	—		7/18	—		12/1	+			3/9	++		—		5/1	—		—	
11/3	—		7/22	—		12/5	+++			3/10	++++		+[3]		5/2	—		—	
11/7	—		7/25	—		12/7	++	—	—	3/11	—		—		5/3	—		—	
11/10	—		7/29	—		12/9	++			3/12	++		+	+	5/4	—		—	
11/14	—		8/1	—		12/12	—			3/13	+++		+[1]	—	5/15	—		—	

[1] = 1 colony, [2] = 3 colonies, [3] = 13 colonies.



These four patients had advanced lesions. In three thoracoplasty was recently performed (case 3 in autumn 1953, cases 1 and 2 at the beginning of 1954) and in case 4 the same operation is pending. All had received treatment with streptomycin, INH and PAS in various combinations for a variable period of time (Table I-IV). In each case tubercle bacilli could be demonstrated—often in great profusion—by direct microscopic examination of the sputum. Despite this it was not always possible to culture the bacilli in the way that one had expected. Thus, in some cases no growth whatsoever was obtained, while in others only some few colonies were grown, by no means corresponding with the abundance of tubercle bacilli inoculated onto the culture medium. Guinea pig tests often were negative. The tubercle bacilli had thus in these cases lost certain of their characteristics. This is so remarkable, that one must query whether the bacilli really were alive. On microscopic examination they were in appearances and staining properties identical in all respects to live and virulent bacilli. But no conclusion can be drawn from this since such is the case even with dead tubercle bacilli. It is more remarkable that they appeared, often plentifully in the sputum, just at a time when the pulmonary lesions were radiologically and clinically highly active, exudative and progressive, and in one (case 3) coincident with the development of a cavity. The only reasonable interpretation of this is that the bacilli were alive and pathogenic to man. This does not, however, exclude the possibility that they could be apathogenic to guinea pigs. It should be remembered, for example, that both human and bovine tubercle bacilli are strongly pathogenic to guinea pigs, while only bovine tubercle bacilli are able to produce progressive tuberculosis in rabbits.

The modified culture and pathogenic properties of the tubercle bacilli is probably best understood as a *parallel phenomenon* to the bacillary resistance that can develop in the course of chemo-antibiotic therapy. Resistance is, therefore, not a prerequisite for the development of this modification. This is evident, in that the tubercle bacilli in the four cases proved to be highly sensitive to streptomycin, INH and PAS in repeated tests. Only once resistance to PAS was suggested. At this time, however, several other cases at the clinic showed resistance to PAS, who on renewed testing proved to be still highly sensitive to PAS; it is therefore possible that it was the same in this case.

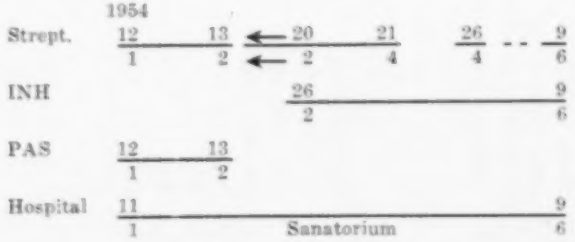
The modified culture and pathogenic properties of the tubercle bacilli are not, of course, necessarily a result solely of chemo-antibiotic therapy. The patient's innate and acquired resistance against tubercle bacilli, as well as the preparation of the sputum with sulphuric acid, play a part. But this does not explain why this modified type of tubercle bacillus is more frequently met in recent times. *In my opinion chemo-antibiotic therapy is largely responsible.* It is not known which agent or which combination of specific therapeutic agents, is the main causative factor. My own material is, of course, far too small to allow any conclusions. But the question is of such interest that it deserves closer study. It should also be ascertained whether the modified properties of the tubercle bacilli

TABLE IV

Case 4. S.N. born Aug. 3, 1902.

Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum			Date	T.B. in Sputum		
1954	Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation		Direct Examination	Culture	Guinea pig Inoculation
1/12	—			2/23	+++	I+	T+	4/7	++	—	+	4/26	++	—		5/12	++	—	—
1/14	++++			2/24	—			4/8	++	+	+	4/27	++	—	—	5/14	+		
1/15	++++			2/27	—			4/9	+++	—		4/28	++	—	—	5/15	—		
1/16	+++			3/3	—			4/10	++	—		4/29	++	—	—	5/19	—		
1/20	++++	pos.		3/6	+++			4/12	+++	—		4/30	++	—	—	5/26	++		
1/23	++++			3/10	+++			4/13	++	+		5/3	++	—	—	5/29	—		
1/27	+++			3/13	++			4/14	++	+		5/4	++	—	—	5/31	—		
1/30	++++			3/17	++			4/15	++			5/5	++	—	—	6/2	—		
2/3	++			3/20	++			4/20	++			5/6	+	—	—	6/5	—		
2/6	—			3/24	++++	pos.		4/21	—			5/7	++	—		6/9	—		
2/9	++++			3/27	++++			4/22	+	—		5/8	++	+[1]	—				
2/13	+++			3/31	+++			4/23	—	—		5/10	+	—	—				
2/20	—			4/3	+++			4/24	++			5/11	—	—	—				

[1] = 1 colony.



are permanent or whether they are reversed some time after the cessation of treatment.

For the time being it suffices to state that culture and guinea pig tests of the sputum, during treatment with chemo-antibiotic agents, are not of the same value as before since they may be negative despite even an abundance of tubercle bacilli in the sputum. The bacilli are certainly pathogenic to man. Planned surgical or other therapeutic measures should, therefore, be carried out without regard to whether the bacilli are pathogenic to guinea pigs.

SUMMARY

1. During chemo-antibiotic therapy of pulmonary tuberculosis bacilli may become resistant to the agent (or agents) employed. They may also become so profoundly modified that they become impossible, or difficult, to culture. The growth, if any, often consists merely of a few colonies which do not correspond to the abundance of the bacilli inoculated onto the medium. Often the guinea pig tests are also negative, or the guinea pigs show only slight lesions.

2. The development of resistance and of modified culture and pathogenic properties of tubercle bacilli is not necessarily simultaneous. (Resistance against the chemo-antibiotic agents employed did thus not develop in any of the cases described.) These merely constitute different expressions of the influence of specific therapy on the bacilli.

3. While the modified tubercle are apathogenic to guinea pigs, they are nevertheless pathogenic to man. Progression of pulmonary lesions may therefore be observed concurrent with their appearance in the sputum. They are most probably quite as dangerous to contacts as are ordinary tubercle bacilli.

4. Culture and guinea pig tests during chemo-antibiotic treatment are not of the same value as before, since these tests may become negative despite even an abundance of tubercle bacilli in the sputum.

5. Planned surgical and other therapeutic measures should not be postponed, but proceeded with just as if dealing with ordinary tubercle bacilli.

RESUMEN

1. Durante la quimioterapia de la tuberculosis los bacilos pueden volverse resistentes al agente o agentes empleados. Pueden aún modificarse tan profundamente que resulte imposible o difícil cultivarlos.

El crecimiento de las colonias si existe, consiste en unas pocas de ellas que no corresponden a la abundancia de los bacilos sembrados en el medio. A menudo las inoculaciones al cuy son también negativas o sólo muestran ligeras lesiones.

2. El desarrollo de resistencia y de los cambios en los cultivos y las cualidades patogénicas del bacilo de la tuberculosis no son obligadamente simultáneas. (La resistencia contra los agentes quimio-antibióticos empleados así, no se presentó en ninguno de los casos descritos). Estos sólo constituyen diferentes manifestaciones de la influencia de la terapia específica sobre el bacilo.

3. Si bien los bacilos son no patógenos para los cuyes si lo son para el hombre. Evolución de las lesiones pulmonares puede por tanto observarse

al mismo tiempo que aparecen esos baclios modificados en los esputos. Estos bacilos son probablemente tan peligrosos para los contactos como lo son los bacilos de la tuberculosis ordinarios.

4. Los cultivos y las inoculaciones durante la quimio-antibioterapia ya no son del valor que antes, puesto que estas pruebas se hacen negativas a pesar de una abundancia de bacilos en los esputos.

5. Los planes quirúrgicos y otras medidas terapéuticas no deben posponerse sino que debe procederse en los casos como si se tratara de bacilos ordinarios.

RESUME

1. Au cours du traitement chimio-antibiotique de la tuberculose pulmonaire, les bacilles peuvent devenir résistants à l'égard des produits utilisés. Ils peuvent subir également des modifications si profondes qu'il devient impossible ou difficile de les cultiver. Leur développement dans le tube de culture, s'il a lieu, ne comporte souvent qu'un petit nombre de colonies, sans correspondance avec l'abondance de l'inoculum ensemencé. L'inoculation au cobaye est également négative, ou ne détermine que des lésions lêgères.

2. L'apparition de la résistance d'une part, et d'autre part la modification de la culture et des propriétés pathogènes du bacille de Koch ne sont pas nécessairement parallèles (dans aucun des cas étudiés par l'auteur, ne s'était constituée une résistance bactérienne). Ces différentes modifications du bacille ne sont que différentes expressions de la façon dont il répond à la térapeutique spécifique.

3. Bien que les bacilles de Koch ainsi modifiés ne semblent pas être pathogènes pour le cobaye, ils n'ont pas pour cela perdu leur action à l'égard de l'homme. En conséquence, malgré l'apparition dans les crachats de bacilles de cette catégorie, il est possible de constater l'extension des lésions pulmonaires. Ils sont vraisemblablement aussi dangereux au point de vue de la contagion que les bacilles tuberculeux communs.

4. La culture et l'inoculation au cobaye au cours du traitement chimio-antibiotique n'ont plus maintenant la valeur qu'elles avaient autrefois, car ces épreuves peuvent se montrer négatives, malgré l'existence de bacilles abondants dans les crachats.

5. Il n'y a donc pas lieu de remettre une opération chirurgicale ou un autre traitement décidé lors de la constatation de bacilles modifiés. Il faut agir exactement comme s'il s'agissait de bacilles de Koch véritables.

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Tumors of the Ribs*

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The object of this paper on tumors of the rib is three-fold. First, to point out that many of them are not metastatic, secondly, that primary malignant tumors are not more frequent than benign tumors, and thirdly, to present some exemplary conditions one should consider in the differential diagnosis of rib tumors. The present review covers the contributions on primary rib tumors through 1953 and comprises a study of 212 cases, seven being added to the 205 cases reported last year.

Much can be learned about these cases from a detailed history, a comprehensive physical and laboratory examination, and the broader utilization of roentgenography in the study of the local area. It is of the utmost

TABLE I—Pathology of 212 Collected Cases of Primary Tumor of the Rib.

	Number of Cases	Per cent of Benign Tumors	Per cent of All Tumors
BENIGN TUMORS	111		52.36
Chondroma	25	22.5	11.8
Osteochondroma	15	13.5	7.1
Myxochondroma	2	1.8	0.9
Osteoma	4	3.6	1.9
Osteoid osteoma	2	1.8	0.9
Osteofibroma	2	1.8	0.9
Fibrous dysplasia	35	31.5	16.5
Hemangioma	8	7.2	3.8
Xanthomatous giant cell	10	9.0	4.7
Miscellaneous—myxoma, solitary myeloma, xanthoma, lipoma, fibroma, chondromyxoid fibroma	8	7.2	3.8
		Per cent of Malignant Tumors	
MALIGNANT TUMORS	101		47.64
Chondrosarcoma	36	35.6	17.0
Osteogenic sarcoma	6	5.9	2.8
Fibrosarcoma	12	11.9	5.6
Mixed sarcomas	8	7.9	3.8
Endothelioma (Ewing's tumor)	25	24.8	11.8
Giant cell	1	1.0	0.5
Miscellaneous—myeloma, lymphosarcoma, reticulum cell, hemangioendothelioblastoma, hemangiosarcoma, liposarcoma	13	12.9	6.1

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importance to the patient to decide clinically whether the tumor is an expression of a local disease or a secondary deposit, whether the growth is simply one in juxtaposition to the rib or whether the lesion is a local manifestation of a systemic disease. To this end, three illustrative cases are presented.

Case 1: Concerns C. S., a 58 year old man who was well until about two months before he was admitted to a hospital. At that time he complained of pain in the upper part of the left side of the chest and shoulder. Sedatives were given for the pain. Roentgenographic studies of the chest and left shoulder were taken and he was discharged several days later with a diagnosis of "neuritis." About a week later, he was admitted to another hospital where a history was obtained of loss of weight and appetite antedating the onset of pain about the left shoulder region. The physical examination at this time was non-revealing except for some tenderness in the upper part of the left side of the chest laterally and in the splenic area. A roentgenographic examination of the chest, Fig. 1A, revealed a tumor opposite the fourth intercostal space posteriorly with involvement of the fourth rib locally. In a detailed examination, a roentgenographic study of the gastrointestinal tract was performed. This disclosed a malignant lesion in the colon. Because of the pain in the chest, a palliative resection of the local area was done. At the same time, the fourth and fth intercostal nerves were removed. The pathologist reported the tumor, Fig. 1B, as a metastatic papillary adenocarcinoma.

Case 2: J. M., a 49 year old man, entered the hospital complaining of pain on the right anterior part of the chest of about six months' duration. The physical examination was essentially negative. A roentgenographic study of the chest, Fig. 2A, revealed a density in the right hemithorax opposite the eighth intercostal space. The eighth rib posteriorly, proximal to the lesion, showed some narrowing. Lateral roentgenograms located the tumor in the posterior part of the thorax. Roentgenographic restudy of the chest after the induction of pneumothorax showed the tumor to be within the chest wall, Fig. 2B. At the time of surgical removal of the lesion, it was noted that the tumor, Fig. 2C, arose from the eighth intercostal nerve. The pathologist reported the tumor as a neurofibroma.

Case 3: A. S., a 57 year old man, entered the hospital because of pain in the right infrascapular area of about three weeks' duration; weakness, loss of appetite, and loss of weight had been present for about six weeks. On physical examination, there was noted a marked pallor, signs of recent loss of weight, and tenderness in the right infrascapular area. The admission blood count showed a hemoglobin of 40 per cent with 1,850,000 red blood cells per cubic millimeter, 5,400 white blood cells, and a relatively normal differential count. An x-ray study of the chest, Fig. 3A, showed a defect and opacity in the posterolateral part of the sixth rib on the right side. There was also noted rarefaction of the medial and lateral parts of the clavicle on the same side. The urine was positive for Bence-Jones protein. Roentgenographic examination

FIGURE 1A

FIGURE 1B

Figure 1A: Tumor in the left fourth intercostal space posteriorly with partial destruction of the fourth rib.—*Figure 1B:* Resected fourth and fifth ribs with intervening neoplastic tissue. Diagnosis: metastatic tumor.

of other bones showed infiltrative changes characteristic of multiple myeloma. At necropsy a rib was removed, Fig. 3B. This showed the changes associated with multiple myeloma.

In these three cases, had the history, physical examination, and x-ray studies been incomplete, at least two of the three would have been treated as primary rib disease until proved otherwise. Granting that in some instances it is not possible to make a definitive diagnosis before the tissue is examined, it does not relieve us of responsibilities to the patient. Having decided that the tumor is primary in the rib, one should leave it to the pathologist to decide whether the growth is benign or malignant, although one can make a reasonably correct diagnosis of the nature of the tumor from the history, physical examination, and roentgenographic studies. What is more important clinically is to decide whether the patient would benefit from the surgical removal of the tumor.

In discussing the pathology of primary tumors of the rib, it is well to remember that the ribs are mesodermal in origin and contain practically all the elements known to be derived from that tissue. In a study of 212 cases collected from various sources,

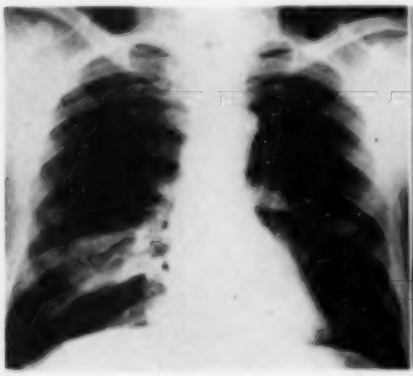

FIGURE 2A

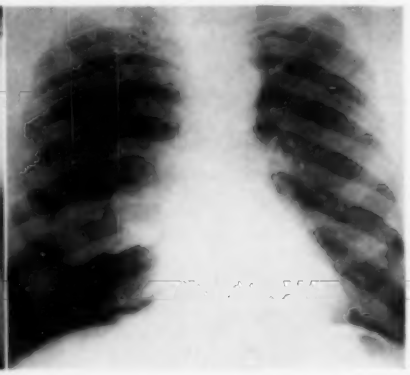

FIGURE 2B

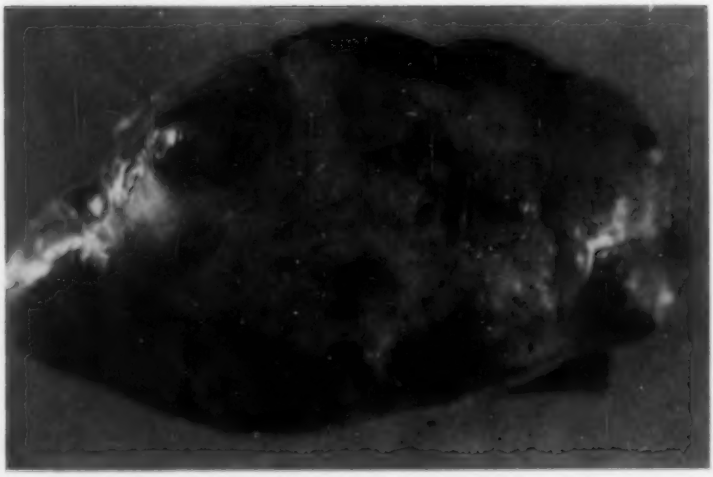

FIGURE 2C

Figure 2A: Tumor in the eighth intercostal space posteriorly on the right side. There is some local thickening of the periosteum on the eighth rib.—*Figure 2B:* Induction of pneumothorax discloses that the neoplastic process is extrapulmonary.—*Figure 2C:* Extirpated tumor. A neurofibroma of the eighth intercostal nerve.

FIGURE 3A

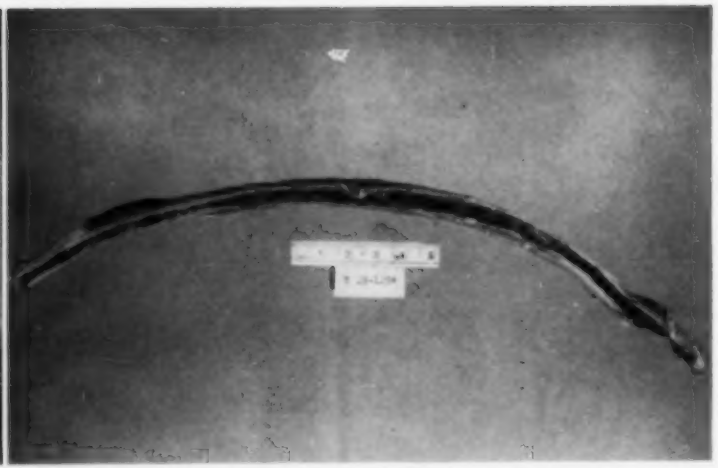

FIGURE 3B

Figure 3A: Tumor on the right side of the chest wall with partial destruction of the posterolateral part of the fifth rib. The medial part of the right clavicle is expanded.—*Figure 3B:* A rib removed at the time of necropsy. The gross changes are characteristic of multiple myeloma.

there were 111 (52.36 per cent) benign and 101 (47.65 per cent) malignant tumors, Table I. The most frequently reported benign tumor was the fibrous dysplasia occurring in 31.5 per cent of the cases, the chondroma was encountered in 22.5 per cent of the cases, and the osteochondroma in 13.5 per cent. Of the malignant tumors, 35.6 per cent were chondrosarcomas, 24.8 per cent Ewing's tumors, and 11.9 per cent fibrosarcomas.

The clinical manifestations of a primary tumor of the rib depend upon (1) location, (2) manner of growth, (3) rate of growth, and (4) secondary effects on surrounding and distant tissues. Not infrequently, these tumors are completely asymptomatic and are discovered on "routine" physical or roentgenographic examination of the chest.

Case 4: J. G., a 19 year old girl, had a pre-employment x-ray film of the chest. A tumor was noted on the fourth rib anteriorly on the left side, Fig. 4A. The physical examination was negative. Even when her attention was called to the tumor, she maintained that it was devoid of symptoms. The tumor was removed, Fig. 4B, and reported by the pathologist as an osteochondroma.

In other instances, the patient's first symptom, and often the only symptom, is an awareness of a growing mass on the chest. The rate of growth varies from patient to patient. Benign tumors often grow slowly, while malignant ones generally tend to grow more rapidly. Case 5 concerns M. P., an 18 year old man. Although he was aware of the presence of the tumor for about three years, he did not observe any

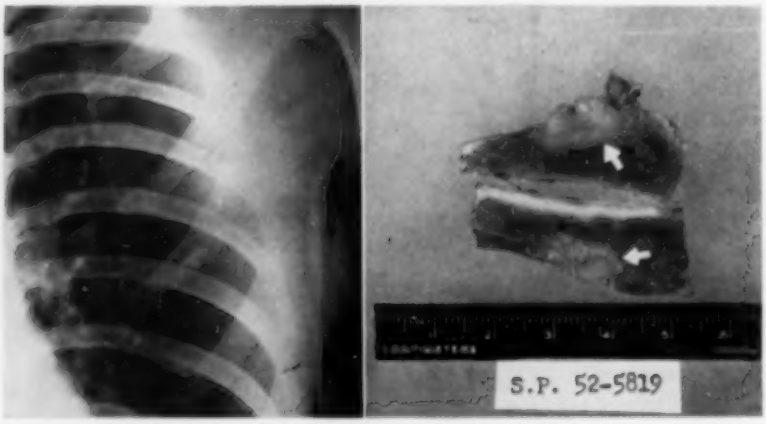

FIGURE 4A FIGURE 4B

Figure 4A: An expanded lesion within the anterior part of the left fourth rib. There is some ossification in the growth.—*Figure 4B:* The opened specimen of the tumor (osteochondroma) and part of the rib.

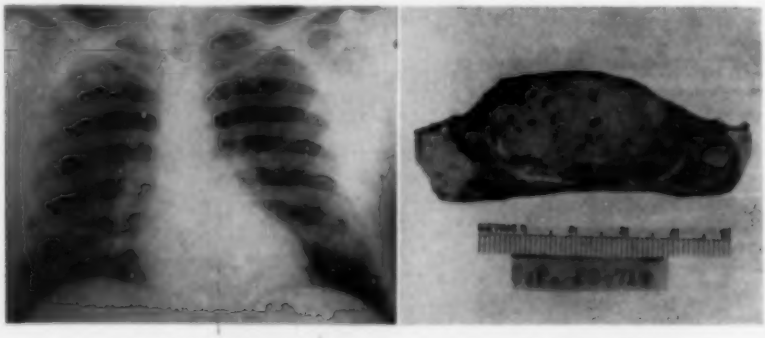

FIGURE 5A FIGURE 5B

Figure 5A: Tumor of the fifth anterior rib on the right side of the chest.—*Figure 5B:* Neoplasm (osteochondroma).

appreciable increase in its size until a few months before entering the hospital. Concomitantly with the increase in size of the tumor, he also observed some sensitivity of the region surrounding the tumor mass. Except for the presence of a mass on the right anterior chest wall which was fixed to the underlying rib, and some tenderness to pressure locally, the physical examination was essentially negative. An x-ray study of the chest, Fig. 5A, revealed a tumefaction on the anterior part of the fifth rib on the right side. The tumor was removed, Fig. 5B, and was reported by the pathologist as an osteochondroma.

The third group of patients who seek the attentions of the physician are those who have pain, either locally or referred to neighboring or distant structures. Case 6 is that of A. L., a 31 year old woman, who sought medical advice because of increasing pains in the upper posterior part of the left side of the chest for about two years. Except for some tenderness in the upper left paravertebral area, the physical examination was non-revealing. A roentgenographic examination of the chest, Fig. 6A, disclosed a multicystic area in the expanded medial portion of the third rib posteriorly. This was removed, Fig. 6B, and the pathologist reported an hemangioma of the rib.

Thus, here are three patients with benign tumors of rib with different manifestations of the presence of the neoplasm. As in these cases, so, too, in the malignant tumors the symptomatology is variegated. Neither is the duration of symptoms any index of the histopathologic nature of these tumors. In the 212 cases, the duration of symptoms in the 111 benign tumor cases varied from absence of symptoms to 30 years, while in the 101 malignant cases, it ranged from three days to 20 years. Pain and/or tumefaction are the commonest symptoms encountered in patients with primary tumors of the rib, regardless of whether they are benign or malignant. Therefore, one cannot draw any conclusion as to the nature of the tumor from the duration of symptoms, or symptoms alone. However, the tendency is for the patient with a malignant tumor to seek medical care earlier than one who has a benign tumor because of the more rapid expansion and more persistent and/or severe pain in the area of the tumor. The age of the patient is no criterion upon which to base a diagnosis of benignity or malignancy, although endothelioma, round-cell sarcoma, plasma-cell sarcoma, and lymphosarcoma are commoner in patients below 30 years of age.

Roentgenographic studies of the tumor site do not reveal conclusive evidences as to the nature of the tumor. However, in a general way it may be said that a tumor confined to a single rib is more likely to be benign than malignant. At the same time, it must be remembered that at its inception a malignant tumor is confined to a single rib before it extends to others. Thus, the presence of a tumor in one rib does not necessarily imply that it is benign. That benign tumors of the rib may involve more than a single rib is well illustrated in the case reported by Poppe and Berg. Consequently, a definitive diagnosis cannot be made from x-ray studies of the ribs alone.

A condition which simulates a primary rib tumor and must be considered in the differential diagnosis is the eosinophilic granuloma. It is the concensus of opinion of pathologists that this lesion is inflammatory rather than neoplastic. Since Lichtenstein and Jaffe (1940) described this condition as a clinical entity, several eosinophilic granulomas of the rib have been reported. These investigators pointed out that this condi-

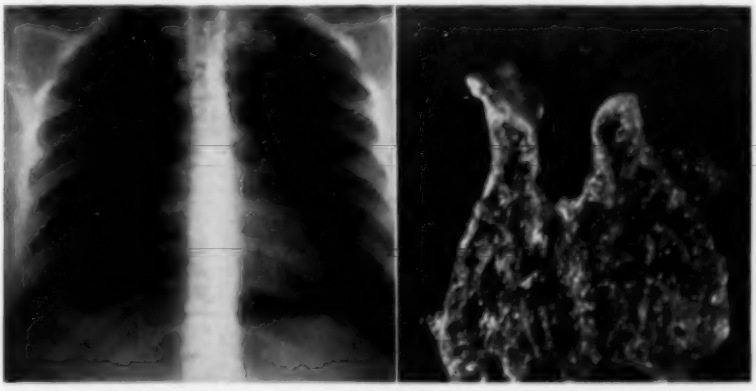

FIGURE 6A FIGURE 6B

Figure 6A: Tumor of the third rib posteriorly on the left side.—*Figure 6B:* Tumor (hemangioma) removed.

tion is an acute manifestation and variant of the basic bone conditions known as Letterer-Siwe disease (nonlipoid histiocytosis) and Hand-Schiller-Christian disease (lipogranulomatosis). Although about 50 patients with eosinophilic granuloma of bone have been reported to date, only 10 involving ribs have been reported thus far. In one of these cases the disease also involved the teeth and lungs (Kruger, Prickman and Pugh). The writer has encountered two patients with eosinophilic granuloma of the rib.

Case 7 is that of G. S., a 14 year old girl, who was well until about two weeks before entering the hospital. At that time she noticed a painful and growing mass on the lower part of the left side of the chest. Physical examination was negative except for a tender mass in the lower lateral part of the chest wall. An x-ray film of the area, Fig. 7A, disclosed an expanded lesion within the 10th rib laterally, thickening of the periosteum with subperiosteal new bone formation. The blood count and sedimentation rate were not contributory to the diagnosis. The rib was removed, Fig. 7B, and was reported as an eosinophilic granuloma.

Case 8 concerns M. G., a 51 year old man, who complained of pain in the lower left thoracic area for many weeks. His initial symptoms were pains after meals and on deep breathing. About six weeks before entering the hospital he began to notice a sensitivity in the posterolateral part of the left lower thorax which was more or less constant and unrelated to meals or breathing. At the time of admission to the hospital, the physical examination was negative except for tenderness to pressure in the

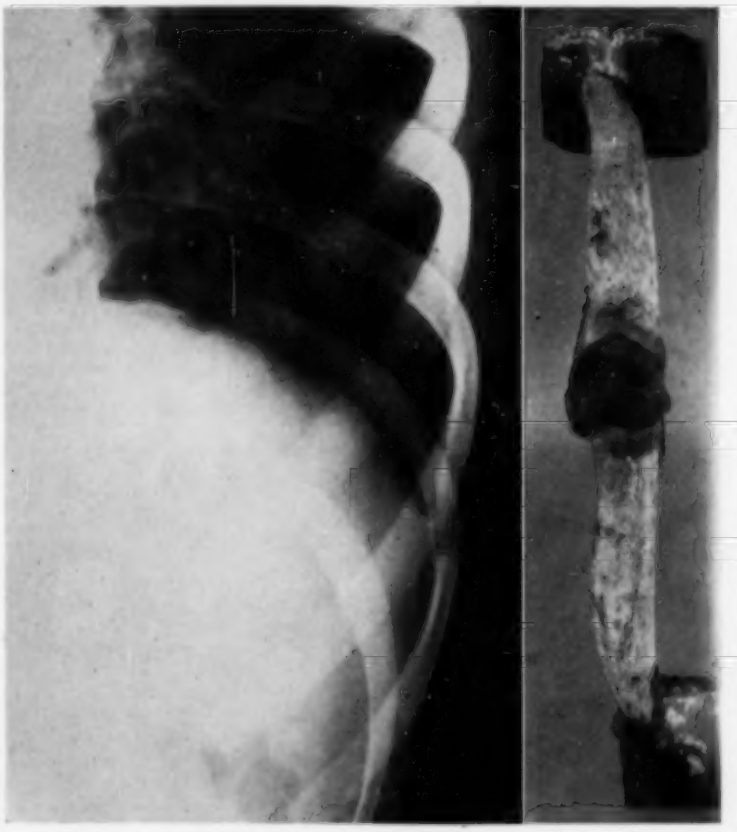

FIGURE 7A FIGURE 7B

Figure 7A: Tumor of the tenth rib on the lateral portion of the left hemithorax.—*Figure 7B:* Tumor (eosinophilic granuloma) removed.

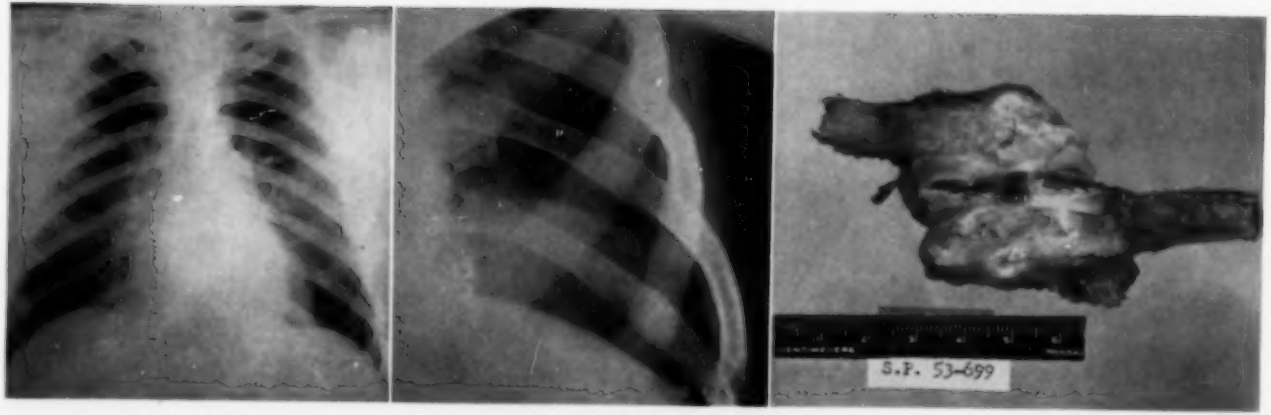

FIGURE 8A FIGURE 8B FIGURE 8C

Figure 8A: Tumor of the eighth rib on the posterolateral part of the left side of the chest. In addition, there is an opacity above the left diaphragm and lateral to the left border of the cardiac shadow.—*Figure 8B:* Partially oblique study of the left supradiaphragmatic area revealing the tumor in the rib and the supradiaphragmatic opacity. —*Figure 8C:* Opened specimen of the tumor (eosinophilic granuloma) of the rib.

lower posterolateral part of the left hemithorax. An x-ray film of the chest, Fig. 8A, showed a tumefaction in the posterolateral part of the eighth rib on the left side. In addition, there was an opacity along the left border of the heart. Roentgenographic restudy of the lower part of the chest in the partially rotated position, Fig. 8B, revealed an opacity above the left diaphragm and the rib findings as noted. The blood studies were non-revealing except for a moderate leukocytosis (11,500) with an essentially normal differential count. He was explored and the involved part of the rib was removed, Fig. 8C. The cause of the supradiaphragmatic opacity was found to be a herniation of omentum through the diaphragm. The report of the pathologist on the rib was an eosinophilic granuloma.

Although a low-grade fever, an increase in sedimentation rate, and multiple sites of involvement suggest an eosinophilic granuloma, a definitive diagnosis cannot be made without biopsy of the tumor. Being an inflammatory lesion, it is supposed to subside in due time. However, there is the question of how long one should neglect the tumor, for in watchful waiting one may be delaying the care of a patient who has a neoplasm of the rib, rather than an eosinophilic granuloma.

In a review of the literature on the subject of noninflammatory primary tumors of the rib one gains the impression that many writers believe most of them to be malignant. This view is not corroborated by statistics. However, it does corroborate the view of other investigators that these tumors are potentially malignant and should be removed as soon as possible. At the time of surgical intervention, one may encounter a well delimited and even encapsulated tumor which has all the appearances of a benign tumor, but which upon histologic examination is found to be malignant. Local invasion of the tissues, or extension outside of the periosteal bed, at the time of the operation, should be considered as a sign of malignancy until proved otherwise.

In a number of cases of primary rib tumors, there is reason to believe that a preexisting benign lesion antedated the malignant lesion. Condon and Harper reported a case in which a tumor of the rib was present for 13 years before it was removed and proved to be malignant. Just as one is often unable to determine the nature of the tumor by simple gross inspection, so, too, may one be unable to determine the degree of maturity from simple microscopic examination of a single section of the tissue. After the removal of a tumor from a rib, Johnson submitted sections to pathologists for diagnosis. The reports are worthy of note: Fifty-four called it an osteogenic sarcoma, six described it as a chondrosarcoma, 27 believed it to be an osteoidosteoma, three thought it was a fibrous dysplasia, four called it healing bone with foreign body reaction, one described it as osteoid tissue forming a tumor, and another thought it was an aneurysmal bone cyst. If these pathologists were at such variance, it is readily understandable why the surgeon is unable to make a definitive diagnosis at the operating table as to whether the tumor is benign or malignant. It may also account for the number of instances in which "benign" tumors have been described as having undergone "malignant" transformation soon after the original extirpation.

CONCLUSIONS

1. Primary rib tumors are as frequently benign as they are malignant.

2. Whether the tumor is benign or malignant is often a difficult decision unless careful and detailed studies are made grossly and microscopically.

3. All primary tumors of the ribs should be removed regardless of whether they are thought to be benign or malignant, unless contraindications exist to surgery.

CONCLUSIONES

1. Los tumores primarios de las costillas son tan frecuentemente benignos como malignos.

2. Es a menudo difícil determinar si un tumor es maligno, o benigno a menos que se hagan estudios minuciosos macro y microscópicamente.

3. Todos los tumores primarios de las costillas deben extirparse sin tener en cuenta que se piense que sean benignos o malignos.

Some of the material contained in this article was previously published in Archives of Surgery (1953). Case 2 was previously published in Annals of Surgery (1953). The foregoing is presented here with the permission of the editors of these journals.

RESUME

1. Les tumeurs primitives des côtes sont aussi fréquemment bénignes que malignes.

2. Il est nécessaire que des études macroscopiques et microscopiques attentives et détaillées soient faites pour classer la tumeur, ce qui est parfois difficile.

3. Toutes les tumeurs primitives des côtes devraient être extirpées, sans tenir compte de leur caractère bénin ou malin.

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Hemorrhage in Pulmonary Tuberculosis as a Surgical Emergency

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Fatalities from exsanguination in pulmonary hemorrhage are rare. Immediate fatalities occur as a rule by clot formation within the bronchial tree and asphyxia, but the sequellae with extension of the disease are more to be feared. Homolateral spread involving the lower lobe is favored by posturing the patient on the side from which the hemorrhage comes. Even more serious is contralateral spread which may convert a unilateral problem into bilateral disease with limitation or delay of surgical treatment.

Various authors[1, 2, 3] have listed hemorrhage as one of the indications for pulmonary resection. In 1950 Ryan[4] reported a case of tuberculosis in a young man who had repeated episodes of pulmonary hemorrhage over a period of several months and intermittent hemorrhage for about two weeks prior to the decision to do right pneumonectomy. This patient made excellent recovery. Ross[5] reported right pneumonectomy for pulmonary hemorrhage in 1953, in a 45 year old woman. The hemorrhage had persisted for four days, bringing the hemoglobin to 51 per cent. Five days later severe hemorrhage began again and pneumonectomy was carried out. Postoperatively the patient was given chemotherapy with satisfactory recovery.

Severe pulmonary hemorrhage, when from well localized pulmonary lesions, should be treated as an emergency by surgery whether the basic pathology be lung abscess, tuberculosis or some other condition. Thoracic surgical techniques have now advanced so that under certain circumstances, pulmonary hemorrhage may be treated by resection on the same principle that severe hemorrhage from gastric ulcer has come to be treated by emergency gastrectomy.[6] The corollary of the surgical approach to the treatment of severe pulmonary hemorrhage has been too much neglected. The usefulness of chemotherapy has changed the operability of pulmonary tuberculosis so the presence of this infection is not a contraindication to surgical excision of the diseased segment or segments if hemorrhage occurs.

Since hemorrhage carries with it the frequent and serious sequellae of spread of the disease into other lobes of the lung, pneumothorax was frequently performed to control it. More recently this therapeutic procedure was replaced by pneumoperitoneum and possibly phrenic phraxis. Thoracoplasty has been done. Lesions which cause hemorrhage are prone to require eventual collapse or resection. It is difficult to prove the efficacy of any procedure or medication in checking hemorrhage, except the eradication of the lesion.

Presented at the 20th Annual Meeting, American College of Chest Physicians, San Francisco, California, June 17-20, 1954.

FIGURE 1C

FIGURE 1B

FIGURE 1A

At the time of pulmonary hemorrhage, the bronchial blood clot may set up conditions for bronchial ulceration and stenosis, and complete loss of function of that lung may follow (Fig. 1A).

Case 1. L. H.: Male, age 64 had tuberculosis since 1941. His past treatment consisted of a few months of intermittent, poorly controlled bed rest, and streptomycin under an internist, after bouts of hemorrhage, each of which left him with more involvement. Examination at the time of a severe hemorrhage in 1952 revealed bronchial stenosis and apparent complete destruction of the right lung, (Fig. 1B). At this time, but not during acute hemorrhage, pneumonectomy was performed (Fig. 1C). He has had negative sputum for two years and is now working as a salesman. Had he been offered resection during an earlier hemorrhage he would have been concerned enough to accept it at a time when the excision could have been limited to a lobe.

It seems probable that hemoptysis may be from either the bronchial arteries or pulmonary arteries, but that the more copious hemorrhages come from lesions of the branches of the pulmonary artery, eroded within cavity walls.

Case 2. E. A.: A case of pulmonary hemorrhage treated by pulmonary ligation. In 1944 we saw a 26 year old Spanish-American who had right thoracoplasty two years before. Active tuberculosis and bronchiectasis underneath the thoracoplasty was confirmed by bronchograms. He had repeated hemorrhages during the two months prior to operation. The pulmonary artery was isolated and ligated, but pneumonectomy was not completed because of technical difficulties. Postoperatively the sputum converted and remained negative. No further hemorrhage has occurred.

Any hemoptysis of small or moderate degree should alert the physician to the possibility of massive hemorrhage, and elective surgery may be carried out, but should severe bleeding develop, the emergency procedure may be required. Localization of the site of hemorrhage is an essential prerequisite to emergency surgery. The source of gastrointestinal hemorrhage may be more difficult to identify even with the abdomen open, but in chest conditions localization is more definite. Previous x-ray examinations are usually obtainable. Clinicians dealing with tuberculosis classify patients as to potentialities for surgical treatment and may be able to designate the probable origin in case hemorrhage intervenes. With x-ray film follow-up studies of tuberculosis patients the physician may be ready for emergency care in case of severe pulmonary hemorrhage. What segment or segments would be the most likely sources of hemorrhage? At the time of hemorrhage, localization of the site may be aided by physical examination. Final decision may be made at the time of projected surgery by preliminary bronchoscopic inspection of the bronchial tree.

Case 3. S. B.: This 40 year old colored male was well until January 1953. At that time he had a "cold" and following this he had vague aches and malaise. In June 1953 his physician sent him for x-ray films of the chest (Fig. 2A), which showed shadows in the right upper suggestive of tuberculosis. Further studies were not made and he continued to lose strength. His appetite was poor and he lost 20 pounds during the following 10 weeks. There was some increasing cough and expectoration to about one-half ounce of sputum daily. Pain in the right chest developed and another x-ray film was made in mid-August 1953. He stated that he had been having night sweats and sleeplessness. About two weeks before there had been a small hemoptysis.

Physical Examination: He was in poor general condition. His weight was 137, height 68", temperature 97.4, pulse 82, blood pressure 102/76. The skin was wrinkled and dry. Many teeth were carious. There were fine crepitations after cough, and bronchial quality of the breath sounds over the right upper chest. The fluoroscope showed a dense, solid upper lobe shadow on the right with a sharp line of demarcation between this lobe and the remaining lung, indicating possible bronchial obstruction. X-ray film (Fig. 2B) confirmed this finding. A bronchial lavage was reported positive for acid fast bacilli. He was placed on combined chemotherapy, with streptomycin, para-aminosalicylic acid and isoniazid (Fig. 2C). Lobectomy at some future date was planned and discussed with the patient. Two days later he had a hemorrhage starting about 10 A.M. During the three hour interval to the beginning of surgery about 18

ounces of blood were coughed up. The blood count was, hemoglobin 11.4; hematocrit 36.5; white blood cells 6,350; differential 62 segs; lymphocytes 30; monocytes eight.

After anesthesia with demerol, pentothal, nitrous oxide and oxygen had been induced, a bronchoscopic examination was performed. A few cubic centimeters of partially clotted blood were aspirated from the bronchial tree and the lobar bronchus from which the bleeding came was demonstrated to be the right upper. With the patient in the face down position after the intratracheal tube was in place just above the carina, an airway was easily maintained. Small mounts of blood were aspirated by the anesthetist during the first part of the procedure. The posterior approach gave rapid access to the branches of the pulmonary artery to the upper lobe, which were ligated and divided before the dissection and occlusion of the bronchus. The procedure was completed in the retrograde direction as in segmental resections.

Pathology: The right upper lobe weighed 715 grams and was of rubbery consistency. On exploration of the cavity, which measured approximately 2 cm. in its greatest dimension, there was a thrombosed vessel projecting into it. Stained sections reveal the presence of numerous acid fast bacilli in the tissues.

Postoperative course was not unusual. The temperature stayed around 102° F. on the first and second postoperative days, came down gradually and remained normal after the fourth day.

He is now symptom free and x-ray films of the chest (Fig. 2D) are clear. Bronchial lavage cultures are negative. He returned to work as a chauffeur at six months postoperative and is still on combined chemotherapy.

COMMENT

Conceivably, the surgeon will encounter the situation where he cannot distinguish which of two localized lesions is responsible for hemorrhage. If on either lung, it might be necessary to abandon the procedure at the preliminary bronchoscopy. If the lesions are in two lobes of the same lung, both lesions may be resected. Temporary occlusion of a lung segment with a soft clamp may be utilized.

Anesthesia should be so gauged as to provide minimum postoperative depression and narcosis and allow for the possibility of an error in the site of localization.

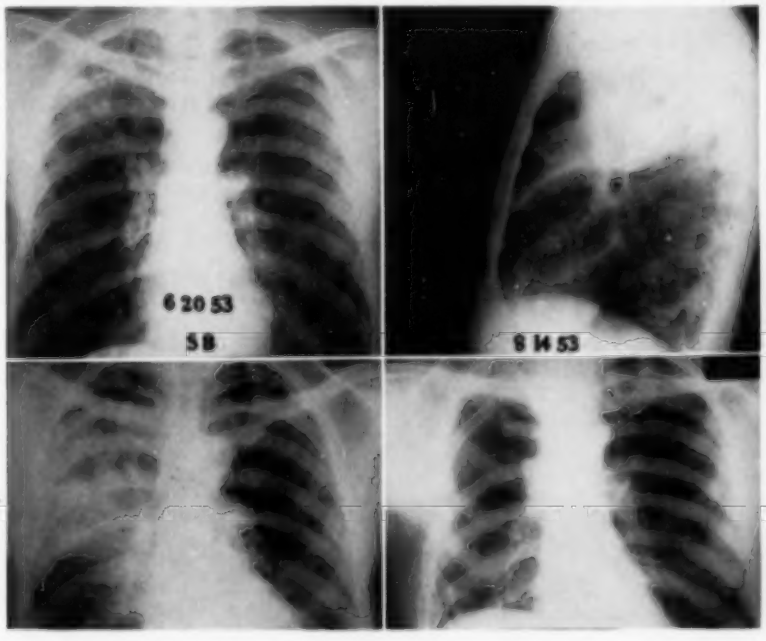

FIG. 2A

FIG. 2B

FIG. 2C

FIG. 2D

It seems probable that amounts of blood encountered during hemorrhage would seldom if ever be too great to be taken care of by the anesthetist with a tracheal tube in place, and the patient in position such as to promote the gravity flow of blood out of the lung.

CONCLUSIONS

1. In a patient who will probably need resection surgery for well localized lesions, the occurrence of severe pulmonary hemorrhage constitutes a surgical emergency.

2. A responsibility of the attending physician in dealing with pulmonary tuberculosis is to consider the surgical possibilities in case massive hemorrhage occurs.

3. The increased risk of surgery during hemorrhage is small compared to the dangers of sequellae in cases of severe hemorrhage in tuberculosis patients.

RESUMEN

1. En un paciente que probablemente necesitará cirugía de resección por lesiones bien localizadas, la presencia de hemorragia pulmonar-constituye una emergencia quirúrgica.

2. Es responsabilidad del médico en tratándose de tuberculosis-pulmonar, considerar las posibilidades quirúrgicas en caso de que ocurra una hemorragia masiva.

3. El aumento del riesgo de la cirugía durante las hemorragias es pequeño, comparado con los peligros de las secuelas en casos de hemorragia severa en pacientes tuberculosos.

RESUME

1. Chez un malade pour iequel il est probable qu'on sera amené à pratiquer une exérèse pour des lésions bien localisées, une intervention d'urgence peut être nécessitée par la survenue d'une grave hémorragie pulmonaire.

2. Lorsque le médecin prend la responsabilité d'opérer après une phase d'attente un tuberculeux pulmonaire, il doit prendre en considération les possibilités chirurgicales si par hasard survient une grave hémorragie.

3. L'accroissement du risque chirurgical lorsqu'une hémorragie est en cours est minime, si on le compare au danger des séquelles que peuvent déterminer les hémorragies graves chez les tuberculeux.

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Industrial Aspects of Bronchiogenic Neoplasms

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Medical students usually learn as the classical example of occupational cancer that scrotal cancer occurred among chimney sweeps in 18th century England.[1] Their attention would perhaps more readily be attracted to the story of lung cancer among miners in the Schneeberg[2] and Joachimsthal mines.[3] The fact that approximately half of all deaths among miners in the latter area resulted from lung cancer establishes the occupational origin of this disease, in at least some cases. Furthermore, the striking increase in frequency of lung cancer and the millions of persons employed in the several 20th century occupations now suspected of having a relationship to the disease confirm the importance of this subject today.

Lung cancer now causes more than 18,000 deaths annually in the United States.[4] Even adjusting for the aging of our population, this represents a four-fold increase during the past two decades.[5] Diagnostic techniques have improved tremendously. But the fact that lung cancer mortality among males has been rising much more rapidly than among females indicates that we are dealing with a real increase in the disease. It now accounts for more deaths than tuberculosis in many states.

Recently attention has focused on cigarette smoking as a cause of lung cancer. Several studies[6] based upon interviews with a series of lung cancer patients and a matched group of "controls" have demonstrated a greater frequency of cigarette smoking, especially heavy cigarette smoking, among the lung cancer patients.

As a further investigation of this question[7] we obtained cigarette smoking histories from 518 lung cancer patients and a like number of matched "controls" in 11 California hospitals. The control group consisted of patients admitted to the same hospitals for conditions other than cancer and other than chest disease—matched for age, sex and race with the lung cancer patients. Tables I and II indicate the similarity of our two groups in respect to biological characteristics. The greater frequency of cigarette smoking, especially in excessive amounts, among lung cancer patients as compared with controls is shown in Table III. In Table IV one may observe that several other measures of the degree of cigarette smoking—age at which began, inhaling, and smoking before breakfast—all confirm that lung cancer patients smoked cigarettes to a greater extent than did the control group. Of particular interest to physicians is that so-called "cigarette cough" occurred among approximately two-fifth of the lung cancer patients; this usually antedated the onset of illness by many years. One

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hundred twenty of the patients stated that they had noted a cough for five years or more whereas only 39 of the control group gave a similar history.

These data, consistent with the other recent well-controlled investigations[6] of the subject, demonstrate a substantial correlation of cigarette smoking and lung cancer. This correlation increases steadily with the amount of cigarette smoking. Levin[8] has most recently assembled the findings of these several studies and, using a method developed by Cornfield,[9] compared the relative prevalence of lung cancer among cigarette smokers and non-smokers. Table V indicates that for men aged 50-59 years lung cancer is four to 11 times as prevalent among smokers as among non-smokers, and seven to 27 times as common among heavy smokers as among non-smokers.

One must accept the conclusion of the New England Journal of Medicine[10] that the evidence for cigarette smoking as a factor in lung cancer is "so strong as to be considered proof within the every day meaning of the word."

TABLE I
AGE DISTRIBUTION OF LUNG CANCER PATIENTS AND CONTROLS

	CASES			CONTROLS
Age	Adeno-carcinoma	Other Types of Carcinoma	Total	Total
Total	46	472	518	518
Under 40	3	22	25	26
40-49	6	56	62	59
50-59	19	194	213	213
60-69	14	154	168	169
70 and over	4	46	50	51

TABLE II
SEX AND RACE DISTRIBUTION OF LUNG CANCER PATIENTS AND CONTROLS

	CASES			CONTROLS
Sex and Race	Adeno-carcinoma	Other Types of Carcinoma	Total	Total
Total	46	472	518	518
Total Male	42	451	493	493
White	41	420	461	461
Negro	....	20	20	20
Other	1	11	12	12
Total Female	4	21	25	25
White	3	15	18	18
Negro	1	3	4	4
Other	....	3	3	3

TABLE III

AMOUNT OF CIGARETTE SMOKING
DURING TWENTY YEARS PRIOR TO STUDY
REPORTED BY LUNG CANCER PATIENTS AND CONTROLS

	CASES		CONTROLS	
Packages of Cigarettes Smoked Per Day	Number	Per Cent	Number	Per Cent
Total	518	100	518	100
None	34	7	124	24
<½	19	4	50	10
½—	71	14	105	20
1—	304	59	199	38
2 or more	80	15	22	4
Not recorded	10	2	18	3

TABLE IV

AGE OF BEGINNING CIGARETTE SMOKING,
SMOKING HABITS AND "CIGARETTE COUGH"
REPORTED BY LUNG CANCER PATIENTS AND CONTROLS

	CASES			CONTROLS		
Cigarette Smoking Characteristics	Number	Per Cent Based on Cigarette Smokers Only	Per Cent Based on Total	Number	Per Cent Based on Cigarette Smokers Only	Per Cent Based on Total
Total	518		100	518		100
Total cigarette smokers	484	100	93	394	100	76
Began 15 years of age	166	34	32	116	29	22
Began 15-24	286	59	55	243	62	47
Began 25 years of age	32	7	6	35	9	7
"Inhale"	449	93	87	327	83	63
"Smoke before breakfast"	373	77	72	229	58	44
"Cigarette cough"	204	42	39	112	28	22

However it is not the sole cause. Some persons with lung cancer deny ever having smoked cigarettes. Levin[11] estimates on the basis of our data that 70 per cent of all lung cancer may be "attributable to smoking." Application of the same method of estimation to other data gives a range of 56 to 92 per cent "attributable to smoking."

In the present and justified concern about cigarette smoking as a cause of lung cancer too little note has been taken of evidence that several occupations may likewise be involved in the etiology of the disease. Unlike the infectious diseases where specific micro-organisms have been identified as the cause, sine qua non, cancer appears to result from a variety of exogenous agents.

The classical studies of the Schneeberg and Joachimsthal miners do not stand alone. Machle and Gregorious[12] found that those employed in cer-

tain chromate ore operations in the United States experienced a 16 times greater mortality for lung cancer than did the general population of the same age-sex distribution. Kennaway and Kennaway[13] using death certificate data for England and Wales noted that metal grinders, workers exposed to road dust, coal gas and tar, asbestos workers, cabinet makers and painters were reported as occupations more frequently among lung cancer patients than would be expected from the general mortality ex-

TABLE V

ESTIMATED PREVALENCE RATES[a] OF LUNG CANCER PER 100,000 MALES OF SELECTED AGES AND VARIOUS CIGARETTE SMOKING HISTORIES[b]

	NUMBER		ESTIMATED PREVALENCE RATES, QUANTITY SMOKED DAILY[c]			RELATIVE PREVALENCE[d]	
	Lung Cancer	Control	Heavy[e]	All Quantities	None	Heavy	All Quantities
Patients aged 50 to 59 years							
Doll and Hill[f]	276	275	94	42	7	13	6
Wynder and Graham[f]	258	210	117	47	4	27	11
Sadowsky, Gilliam, and Cornfield[f]	198	208	87	44	12	7	4
Breslow, Hoaglin, Rasmussen, and Abrams[f]	213	213	102	46	6	17	7
Roswell Park Memorial Institute	173	657	141	109	15	9	7
Patients aged 60 and 69 years							
Doll and Hill[f]	197	199	137	63	0	....	....
Wynder and Graham[f]	187	160	138	70	5	29	15
Sadowsky, Gilliam, and Cornfield[f]	76	71	44	71	5	9	4
Breslow, Hoaglin, Rasmussen, and Abrams[f]	168	169	433	78	17	25	5
Roswell Park Memorial Institute	197	675	479	280	50	9	5

[a]Estimated according to the method of Cornfield.[8]

[b]All data appearing in this table, except for Roswell Park Memorial Institute figures, are taken from the paper by Breslow et al.[3]

[c]Quantity smoked daily, except for the present study, is all forms of smoking expressed as cigarettes with pipes and cigars converted to their equivalents in cigarettes as follows:

Doll and Hill—1 ounce tobacco = 4 cigarettes a day.

Wynder and Graham—1 cigar = 5 cigarettes; 1 pipeful = 2½ cigarettes.

Sadowsky, Gilliam, and Cornfield—1 cigar = 10 cigarettes; 1 ounce pipe tobacco = 20 cigarettes.

For the Breslow et al. study quantity smoked daily includes only cigarette smoking.

[d]Relative prevalence are the following ratios: heavy = rate among heavy smokers/rate among non-smokers; all quantities = rate among smokers/rate among non-smokers.

[e]Heavy smoking is defined as the following number of cigarettes or equivalents of cigarettes per day: Doll and Hill, 50 or more; Wynder and Graham, 35 or more; Sadowsky, Gilliam, and Cornfield, 41 or more; Breslow et al., 40 or more; present study; 20 or more.

[f]Source: Levin, M. L. Etiology of Lung Cancer: Present Status, New York State J. Med., 54:6, p. 770, Mar. 15, 1954.

perience. Information obtained by interview with hospitalized patients in St. Louis and elsewhere in the United States, studied by Wynder and Graham,[14] disclosed that painters and "hot metal workers" stood out as excessive among lung cancer patients as compared with a control group. Mortality experience among industrial policy holders in the Metropolitan Life Insurance Company indicated, according to Lew,[15] several occupations with a higher than average rate from cancer of the lung; Table VI

TABLE VI

"MORTALITY EXPERIENCE AMONG WHITE MALE WAGE EARNERS INSURED UNDER INDUSTRIAL POLICIES IN THE METROPOLITAN LIFE INSURANCE COMPANY 1937-1939: OCCUPATIONS WITH PROBABLY HIGHER-THAN-AVERAGE DEATH RATES FROM CANCER OF THE LUNGS"

Occupational Group	Deaths From All Causes	Deaths From All Forms of Cancer	Deaths From Cancer of Lungs		
			Number	Percentage Relative to Deaths From All Causes	Percentage Relative to Deaths From All Forms of Cancer
All Wage Earners	112,991	13,858	1,682	1.5	12.1
Blacksmiths	503	75	11	2.2	14.7
Brick and Stone Masons*	722	124	18	2.5	14.5
Cooks—Hotel and Restaurant*	345	48	8	2.3	16.7
Coppersmiths, Tinsmiths, Etc.*—Not Roofers	402	61	9	2.2	14.8
Engravers (Metal) and Photoengravers	84	15	5	6.0	33.3
Laundry Workers (Except Laborers)	222	27	5	2.3	18.5
Mail Carriers	242	41	7	2.9	17.1
Miners (Underground, excluding Coal Miners)	222	20	6	2.7	30.0
Painters and Varnishers—House, Shop, etc.	2,821	366	62	2.2	16.9
Plasterers	190	31	5	2.6	16.1
Plumbers, Steamfitters, and Gasfitters*	1,178	156	29	2.5	18.6
Roofers and Slaters*	225	31	5	2.2	16.1
Slaughter and Packing-House Operatives	279	41	7	2.5	17.1
Street Cleaners	336	64	9	2.7	14.1
Tannery Operatives	227	33	5	2.2	15.2
Tailors and Other Clothing Workers	1,564	228	37	2.4	16.2
Traveling Salesman	374	46	10	2.7	21.7
Welders*	216	24	7	3.2	29.2

*In these occupations the mortality from all forms of cancer was somewhat higher than average as follows: Brick and Stone Masons, 155% of average; Cooks—Hotel and Restaurant, 119% of average; Coppersmiths, Tinsmiths, etc.—Not Roofers, 123% of average; Plumbers, Steam Fitters, and Gas Fitters, 110% of average; Roofers and Slaters, 112% of average; Welders, 126% of average.

[15]Lew, E. A., Use of Life Insurance Company Records, for Cancer Studies. Arch. of Ind. Hyg. and Occup. Med., 5:199-203, Mar., 1952.

TABLE VII

CASES AND CONTROLS EMPLOYED FOR AT LEAST 5 YEARS IN SELECTED OCCUPATION GROUPS[1]

	Occupation	PERSONS EMPLOYED IN OCCUPATION AT LEAST 5 YEARS	
		Cases	Controls
1	Welders and sheet metal workers doing welding	14	2
2	Steamfitters, boilermakers, asbestos workers	10	1
3	Electric bridge crane operators—metal industry	5	1
4	Occupations in the extraction of lead, zinc, and copper ore	9	3
5	Marine engineers, firemen, oilers and wipers	12	6
6	Construction and maintenance painters	22	12
7	Cooks, commercial (excluding cannery cooks)	35	21

[1] Occupation groups based on regrouping according to common occupational exposures after detailed examination of records.

shows these occupations. Hueper[16] mentions several exposures suspected of being involved in lung cancer.

Interviews with lung cancer patients and a control series in our study[7] included life-long occupational histories taken by persons skilled in occupational analysis. Information about every occupation in which the person had engaged was so detailed that the session often lasted two hours or more. It covered an exact description of the work, the industry, the duration of employment, known exposures to toxic materials, and other factors. Interviewer bias as to the occupational data can be practically ruled out inasmuch as both lung cancer patients and the controls mentioned hundreds of occupations, none of which was suspected by the interviewers.

Although the information included type of industry and exposure to known toxic agents, efforts to analyze these were not productive. Therefore major emphasis in the analysis went to occupation itself, coded according to the United States Dictionary of Occupational Titles (Second Edition) Washington, D. C.: U. S. Employment Service, 1949. This lists 367 categories.

Table VII presents a list of apparently significant occupations based upon our study. This tabulation was developed by first observing the relative frequency of occupations in which individuals of the case and control series had spent at least five years. This gave leads for further study. Thereafter, since the code used was not designed to reflect common occupational exposures, analysis was carried to the examination of records of individual cases and controls. Regrouping of occupations based upon common exposures resulted in Table VII. It appears that exposure to metallic particles or fumes, asbestos, paint and other materials appear to play some role. Similarity of this list to other studies, particularly that of Lew[15] is immediately apparent.

Comparability of the findings in four studies is shown in Table VIII. These separate investigations, extending over a 20-year period and two

countries, utilized general mortality statistics, life insurance statistics and interviews with hospitalized patients. The fact that such varied data, analyzed in different ways, consistently identify certain occupations attests their probable significance in the development of lung cancer. Besides the occupations listed repeatedly in Table VIII—painting, welding and other metal work, steam fitting and other asbestos work—additional types of work are mentioned frequently in the findings of studies of occupational aspects of lung cancer. These include furnace men, engineers, workers exposed to petroleum and petroleum combustion, carpenters, cabinet makers and wood workers generally.

Thus, several types of employment may constitute etiologic factors in lung cancer. The most clear-cut evidence pertains to the Schneeberg and Joachimsthal mines and to chromate ore operations in the United States; in fact, one can hardly doubt the causative role of work exposure in these groups. Other studies, including our own, strongly implicate the occupations shown in Table VIII: painting, welding and other work involving hot metals, commercial cooking, metal mining, steam fitting and other asbestos work.

We are now engaged in another type of investigation designed to confirm or refute the hypothesis that these latter occupations carry an excessive risk for lung cancer. This involves obtaining information about employment from persons engaged in suspect occupations. It will include cigarette smoking history as well as details about type of work and duration of employment in it. Such information is being assembled for approximately 10,000 persons in the age range 35-64, now employed in each of the suspect occupations listed in Table VII. During the next few years we will observe the mortality experience of these groups through checking

TABLE VIII

CORRESPONDENCE OF FOUR STUDIES IMPLICATING SELECTED OCCUPATIONS IN LUNG CANCER

Kennaway[11]	*Wynder-Graham*[4]	*Lew*[10]	*Breslow, et al*[7]
Painters	Painters	Painters and varnishers—house, shop, etc.	Construction and maintenance painters
Metal grinders	Welders, foundry and steel-mill workers and other "hot metal" workers	Welders, coppersmiths, tinsmiths, etc. blacksmiths	Welders and sheet-metal workers doing welding. Electric bridge crane-operators, metal industry
		Cooks—hotel and restaurant	Cooks, commercial (excluding cannery cooks)
		Miners (underground, excluding coal-miners)	Occupations in the extraction of lead, zinc and copper ore
Asbestos workers		Plumbers, steamfitters and gasfitters	Steamfitters, boilermakers, asbestos workers

with the vital statistics index of the California State Department of Public Health. Thus, the actual lung cancer mortality rates will be determined for persons in occupations identified by previous studies as possibly having etiologic significance. Comparison of the rates with that of the general population of the state (corrected for age-sex distribution) will indicate the degree of excessive risk, if any, in the occupational groups. If their lung cancer mortality rate substantially exceeds the rate for the general population, one may conclude that some occupational exposure is involved. Thereafter it will be necessary to determine the precise environmental agent and undertake preventive measures.

As occupations are identified as causative factors in lung cancer we will be in a better position to establish control of this disease not only by prevention, but also by intensive case-finding efforts in high risk groups.

SUMMARY

Lung cancer has increased strikingly in recent years; it now causes more than 18,000 deaths annually in the United States. Although much evidence incriminates cigarette smoking as a major factor in the disease, it is not the sole cause. Previous studies are cited to indicate the role played by occupational exposure.

Interviews with 518 lung cancer patients in California hospitals, and a like number of non-cancer "control" patients, confirmed the greater frequency of cigarette smoking among lung cancer patients. The interviews also covered life-long occupational history. Analysis of this data disclosed that the following occupational groups appeared with substantially greater frequency among the lung cancer case histories, as compared with the controls: welding and sheet metal workers doing welding; electric bridge crane operators, metal industry; construction and maintenance painters; commercial cooks; occupations in the extraction of lead, zinc and copper ore; steamfitters, boilermakers, asbestos workers; marine engineers; firemen, oilers and wipers. The correspondence of this list of occupations with those arising from other studies of occupational factors in lung cancer is demonstrated.

Further work is underway to confirm or refute the hypothesis that these occupations carry an excessive risk for lung cancer.

RESUMEN

El cáncer del pulmón ha aumentado notablemente en los años recientes; ahora causa más de 18.000 defunciones al año en los Estados Unidos.

Aunque existen evidencias de que el fumar cigarrillos tiene gran responsabilidad en la enfermedad, no es la única causa.

Existen trabajos anteriores que se citan indicando el papel que desempeña la exposición ocupacional.

Las entrevistas llevadas a cabo con 518 enfermos de cáncer del pulmón en los hospitales de California y con un número igual de enfermos de "control" no cancerosos, confirmó la gran frecuencia del cáncer entre los

fumadores de cigarrillos. Las entrevistas incluyeron también las historias ocupacionales de toda la vida. El análisis de estos datos descubrió que los siguientes grupos de ocupaciones mostraron demodo substancial mayor frecuencia entre las historias de cáncer del pulmón en comparación con los controles: trabajadores en soldadura y enlámina de acero, operadores de grúas eléctricas en los puentes, industria de metales, pintores de construcciones y de mantenimiento, cocineros comerciales, trabajados en la extracción de plomo, zinc y cobre de los minerales, trabajadores en máquinas de vapor, constructores de calderas, trabajadores de asbestos, maquinistas marinos, bomberos, engrasadores y limpiadores. La correspondencia de esta lista de ocupaciones con las que resultan de otros estudios de factores de ocupación se demuestra. Está en preparación más investgación para confirmar o refutar la hipótesis de que estas ocupaciones tienen consigo un riesgo mayor conrespecto al cáncer.

RESUME

La fréquence du cancer pulmonaire s'est accrue de façon frappante ces dernières années. Il cause maintenant plus de 18.000 décès par an aux Etats-Unis. Bien que, de toute évidence, on puisse incriminer la fumée des cigarettes comme facteur principal de cette affection, ce n'est pas là la cause unique. L'auteur cite les études antérieures qui ont montré le rôle joué par certains risques professionnels.

L'interrogatoire de 518 malades des hôpitaux de Californie, atteints de cancer pulmonaire, et d'un nombre semblable de malades témoins non cancéreux, confirme la plus grande fréquence des fumeurs chez les premiers. L'interrogatoire porta aussi sur les antécédents professionnels de toute leur existence. L'analyse de ces données a démontré que comparativement au groupe témoin, les professions suivantes figurent avec une fréquence notablement plus grande dans les cas de cancers: soudeurs et ouvriers lamineurs travaillant dans la soudure, conducteurs de grue, ouvriers de l'industrie métallurgique, peintres en bâtiments, cuisiniers, travailleurs s'occupant de l'extraction du plomb ou du zinc, ou des minerais cuivreux, chaudronniers, conducteurs de machines à vapeur, ouvriers exposés à y'amiante, mécaniciens de la marine, pompiers, graisseurs et nettoyeurs. Cette liste de professions est en accord avec celles qui ont été établies au cours d'autres études des facteurs professionnels dans la fréquence du cancer.

Des travaux ultérieurs sont en cours pour confirmer ou infirmer l'hypothèse selon laquelle ces professions comportent un risque de cancer extrêmement important.

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Fibrosarcoma of the Mediastinum

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Rapid development of thoracic surgery has engendered renewed interest in neoplasms affecting the mediastinum. Exploratory thoracotomy has made feasible an accurate histological classification of these tumors, and within the past 13 years substantial contributions have been made in this direction.[4, 5, 6, 15, 25]

Among the benign tumors of the mediastinum the neurofibromas, dermoids and cysts are most common. Thus in Blades[4] series from the army thoracic surgery center including 94 benign tumors, 29 were neurogenic, 23 bronchogenic and 10 pericardial cysts, and 14 were dermoids. Brewer's[6] series of 35 benign tumors included 16 neurofibromas, eight teratomas and five cysts, three bronchogenic and two pericardial.

The relative incidence of malignant mediastinal tumors was more variable. In one group of 64 cases[15] 47 were lymphomas and 17 sarcomas. These latter included three superior sulcus tumors not identified histologically, three lipomas, three neurosarcomas, five malignant teratomas, two malignant thymomas and one apical fibrosarcoma. Twelve of these 17 cases were explored. In six the tumors were inoperable, and in the other six they were removed. Blades[4] material was classified as follows: six malignant teratomas, four Hodgkins, two lymphoblastomas, two thymomas, and one neurosarcoma. Brewer[6] reported in his malignant group two spindle cell sarcomas, one fibroblastic sarcoma, one liposarcoma, one neurosarcoma, three Hodgkins, and one endothelioma.

Confirmed fibrosarcoma of the mediastinum is apparently quite uncommon. None appeared in the original eight cases of Heuer.[31] Andrus[1] report of the 155 cases in the chest tumor registry included seven cases of mediastinal sarcoma, none of which was definitely identified as fibrosarcoma. Single cases were reported by Doege[11] and Robins.[20] One of these[11] was successfully removed without recurrence. Two mediastinal fibrosarcomas appeared as Cabot Cases in the clinicopathological conferences of the Massachusetts General hospital.[8, 9] Heuer and Andrus[15] in reviewing the world literature from 1926-1940 found 32 cases of mediastinal sarcoma, further characterized as follows: 17 fibrosarcoma or fibroblastoma, 13 "sarcoma," one hemangiosarcoma, and one liporhabdomyosarcoma. The authors remarked that these tumors usually occur apically, in the anterior or posterior mediastinum and when arising in nerves may resemble hour-glass tumors. Symptoms were those of compression or involvement of mediastinal structures. Nineteen of the cases were operated upon. In 18 the

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tumor was removed but there were eight post-operative deaths. In seven of the fibrosarcomas removed, death occurred within three months after surgery.

The role of benign tumors in giving rise to sarcoma by malignant degeneration is of considerable practical interest. Heuer[14] was able to cull from the literature 32 cases of mediastinal fibroma. Fourteen of the cases in this group underwent surgery, and 13 recovered. In contrast, all 18 of the non-operated cases died of pressure and compression symptoms. Dolley and Brewer[12] were of the opinion that simple fibromas rarely produce symptoms, and that when pressure phenomena appear, sarcomatous degeneration has occurred. These experiences suggest that early surgical intervention should be a general rule for neoplasia of the mediastinum.

Three cases of mediastinal fibrosarcoma were diagnosed at the Bronx Veterans Hospital in the five year period from 1948-1953. Because of their unique symptomatology, detailed description and discussion appear warranted.

Case 1: This 19 year old white man volunteered for the United States Navy in July 1951, when routine chest x-ray films showed a right-sided mediastinal mass. These films were compared with roentgenograms taken in 1949 and 1950, and the latter were also said to have shown mediastinal enlargement. In December 1951 he experienced gradual onset of shortness of breath. In February 1952 he developed a dry, mostly non-productive cough but occasionally thick mucoid sputum was present. Finally he experienced sputum streaked with bright red blood. For these complaints he was admitted to the Bronx Veterans Hospital on Feb. 12, 1952.

Physical Examination—He was a husky boy with cyanotic tinge to lips and nail beds, increased after walking. The neck veins were distended. The superficial veins were dilated over the right side of the chest. Dullness was present throughout the left side of the chest with bronchophony over the left mid-posterior lung field, and tubular breathing was heard in that area. A systolic blow was heard at the apex of the heart. The liver was felt four finger-breadths below the costal margin but was not tender.

Roentgenograms of the chest demonstrated two lobulated masses extending from

FIGURE 1

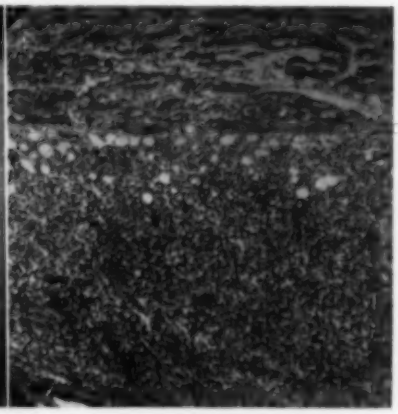

FIGURE 2

Figure 1, Case 1: Admission roentgenogram demonstrating the two large, circumscribed right mediastinal masses. Note the huge cardiac silhouette and obliteration of the left costophrenic sinus by fluid.—*Figure 2, Case 1:* Photomicrograph 100X. The dense, spindle-celled tumor has invaded the pericardial fat and compressed adjacent myocardium.

the right side of the mediastinum into the right hemithorax halfway to the lateral wall. The heart appeared to be greatly enlarged with all chambers participating. A small pleural effusion was seen at the left base. On gastrointestinal series the esophagus was in no way distorted by the extensive thoracic tumor mass. Extrinsic deformity of the duodenum suggested a large periduodenal node. An ECG showed low voltage QRS and T waves compatible with pericardial effusion.

Course in Hospital—The venous pressure was 380 mm. water. No shrinkage of the tumor mass was observed after a test dose of radiation (300r). Needle biopsy of the mass was attempted, and the specimen had the appearance of a spindle cell sarcoma.

Triethylenemelamine (TEM) was given in a dose of 5 mg. on two successive days. In view of symptomatic improvement which enabled him to become ambulatory, TEM was given again after an interval of a month, at first 1 mg. daily for seven days then the dose was raised to 2 mg. a day for seven days. Finally he was receiving as much as 4 mg. of the drug daily for seven days. Again subjective improvement was striking in that he enjoyed a sense of well being, vigor and appetite. His venous pressure declined to 200 mm. of water. Although radiographically little or no change was seen in the tumor mass, the cardiac silhouette shrank markedly. He was discharged on June 25, 1952 on a maintenance dose of TEM 1 mg. daily with close hematological supervision. He had had a total dose of 87 mg. of the drug.

Subsequently he gained weight and was well until December 14, 1952 when he developed shortness of breath, brassy cough and blood stained sputum. He appeared slightly dyspneic. Markedly distended veins were present over the chest and abdomen, and the cervical veins were full and prominent. There were dullness over the right anterior chest and tubular breathing in the left infraclavicular region. The apical rate was regular at 120. In the roentgenogram the huge rt. mediastinal mass was again noted with extension across the midline to the region of the left lung. The superior mediastinal mass obscured the heart and great vessels. The venous pressure was 320 mm. of water.

He again experienced subjective relief from daily TEM in 1-3 mg. dosage. Leucopenia of 3700 and nausea and vomiting necessitated interdiction of TEM on February 16, and subsequently the WBC returned promptly to normal. The total dose of TEM was then 96 mg. Presently cyanosis of the face, upper chest and extremities became pronounced. The tissues were puffy and edematous. On February 21 he complained of pain in the right calf with swelling. Homan's sign was positive. Scleral icterus was noted and this rapidly deepened. He died suddenly while eating in Feb. 1953.

Pathologic Findings

There was moderate cyanosis of the face and fingertips, and the face had an edematous, rounded appearance. There was severe pitting edema of the lower extremities. No adenopathy was present.

A huge tumor mass filled the upper two-thirds of the right hemithorax, enveloping and compressing the right upper and middle lobes, and obliterating most of the right pleural space by adhesions to the chest wall. There was a sharp line of demarcation between tumor and compressed lung parenchyma. In the mediastinum, the mass extended over and obliterated the pericardial space, and encircled the great vessels and major bronchi. Both venae cavae, the aorta and pulmonary artery were thus enveloped. The tumor was greyish-yellow and soft, and on section consisted largely of necrotic tissue and clotted blood. The tumor had penetrated both atria and ventricles, leaving a thin layer of myocardium and endocardium intact. A similar encasement of the supra-valvular aorta, main and right pulmonary arteries was observed. The upper lobe branch of the right pulmonary artery was occluded by thrombus. The superior vena cava was enveloped and partially destroyed by tumor, and could not be traced more than 3 cm. above the right atrium. A similar situation obtained in the inferior vena cava.

Histologically the tumor was typical fibrosarcoma. Necrosis and hemorrhage were prominent. The tumor was quite invasive, and not only com-

pressed the lung but found its way into the perivascular and peribronchiolar lymphatics. In some areas infarction of the lung was seen. There was striking invasion of the heart. The thrombi in the large vessels were organizing blood clots, and did not contain tumor. The mediastinal lymph nodes were the site of extreme edema and congestion, but there was no tumor. There were no distant metastases.

Case 2: A 36 year old white male stage manager was admitted to the Bronx Veterans Hospital on October 30, 1948 complaining of shortness of breath, for three years, and non-productive paroxysmal cough, for four months. In the fall of 1943 he noted the onset of weakness, easy fatigability and exertional dyspnea. In May 1948 he developed severe pharyngitis, chills, fever and slight cough. He was treated with penicillin for right lower lobe pneumonia and responded slowly. In July he developed non-productive cough aggravated by recumbency, and there was accentuation of fatigue and dyspnea. When orthopnea supervened, acute heart failure was diagnosed and he was treated with salt-restricted diet, digitalis, mercuhydrin and bed rest. Again his symptoms worsened, and he was admitted to the hospital with dyspnea, orthopnea, cough, fever and cyanosis.

Physical Examination—He was asthenic and appeared acutely ill. He was cyanotic, tachypneic and had a fever of 102 degrees F. The excursion of the left hemithorax was limited. There were dullness, diminished breath sounds, and rales in the left base, and slight dullness and diminished breath sounds in the right base.

On roentgen examination the transverse diameter of the heart was at the upper limit of normal, but there was marked prominence of the pulmonary artery segment. Both hilar shadows were accentuated. Examination in the left lateral position showed a homogeneous haze in the lower left hemithorax suggesting pleural effusion, which cleared radiographically in four days.

Course in Hospital—He was treated with penicillin, oxygen and digoxin. His fever, dyspnea and cough lessened. The venous pressure and circulation time were normal. There was continued bi-hilar engorgement, more marked on the right, and right pleural effusion appeared late in November. Study at the Bellevue Hospital, Cardiopulmonary laboratory indicated a pattern of chronic pulmonary fibrosis with diffusion barrier, and cor pulmonale. In January 1949 he began to cough up sanguineous sputum, severe enough to reduce the RBC to 2.5 million. The count returned to normal following transfusions. At this time the shadow of a right paratracheal mass appeared on the chest film. It gradually enlarged, projecting into the right apex and mid lung field. Weight loss and weakness were progressive, with periods of dis-

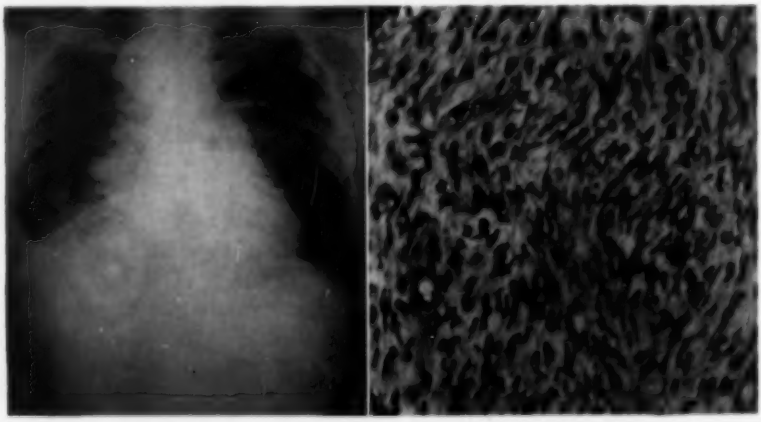

FIGURE 3 FIGURE 4

Figure 3, Case 2: Roentgenogram three months after admission, showing well defined right upper mediastinal mass. Note hilar densities, and right pleural effusion.—*Figure 4, Case 2:* Photomicrograph 440X. Detail of tumor showing parallel, wavy rows of spindly, plump hyperchromatic cells.

orientation and confusion. Systemic venous pressure increased, and likewise hepatomegaly and pretibial edema appeared. Radiation therapy was attempted but the mass was completely resistant. An aspiration biopsy of the mass enabled the diagnosis of fibrosarcoma to be made with assurance. One month before death edema of the right upper extremity and right chest wall appeared and there was distension of the left jugular vein. Angiocardiography showed complete superior vena cava obstruction. Death occurred on April 19, 1949.

Pathologic Findings

The right hemithorax was occluded by firm fibrous adhesions. A huge tumor presented in the right hemithorax, practically involving the entire space, and markedly compressing the right upper lobe. The right internal jugular vein was thrombosed and a large tumor nodule occluded the vessel 3 cm. above the right atrium. Large firm yellow masses of tumor tissue invaded the lower right pleural space, varying from 2 to 10 cm. in size. Necrotic degeneration and cystification of the nodules were not unusual. The pericardium was almost completely invaded by tumor mass, and the pericardial cavity was obliterated by adhesions. The pulmonary artery and its main branches contained a large mass of tumor, and the right main branch was completely occluded. Tumor propagation extended well into the left main branch. There was no gross infiltration of the myocardium. The other organs were normal and no distant lymph node was involved.

Histologically the pleura was tremendously thickened and in places almost completely replaced by tumor tissue. The alveolar septa abutting on tumor were collagenized, resembling the pattern seen in pulmonary fibrosis. The tumor was vascular and contained many large, thin walled vessels. In general the nodules of cellular fibrosarcoma were sharply defined but in places could be seen invading and compressing parenchyma. However, there was no diffuse sarcomatosis to account for the alveolar-capillary block pattern of the pulmonary function studies. The latter ap-

FIGURE 5

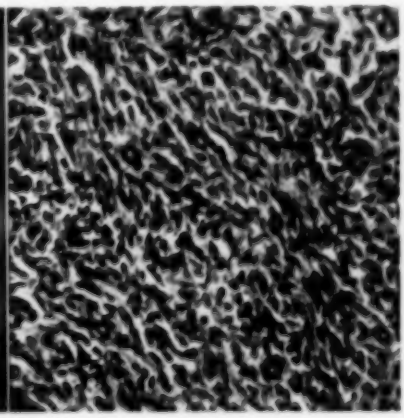

FIGURE 6

Figure 5, Case 3: Admission roentgenogram showing almost complete opacification of the left hemithorax. Note the faintly outlined density in the right paravertebral region.—*Figure 6, Case 3:* Photomicrograph 440X. Detail of tumor showing cellular fibrosarcoma with large hyperchromatic nuclei.

peared related to the chronic pneumonitis and interstitial fibrosis in the portions of lung nearest the tumor.

Case 3: The patient was a 39 year old white male admitted on Sept. 24, 1952. He was well until July 29 when he experienced severe pain in the left side of the chest, aggravated by inspiration, but not associated with cough, sputum or fever. On roentgen examination there was almost complete opacification of the left hemithorax. Thoracentesis on two occasions yielded large quantities of blood, and a tube was left *in situ* for 10 days. He was transfused three times, and felt improved.

A week following discharge from the hospital he had recurrence of pain and dyspnea, and he was again tapped. After a short trial of radiation therapy he sought admission to the Bronx Veterans Hospital.

Physical Examination—He appeared chronically ill, pale, dyspneic and anxious. Positive findings in the chest included flatness up to the clavicle and absent breath sounds on the left. The point of maximum intensity of the cardiac apex was palpated in the fourth intercostal space 2 to 3 centimeters to the right of the right sternal border. The first mitral sound was best heard in this area. Blood pressure was 110/70. There was voluntary guarding over the left side of the abdomen and the liver edge was one fingerbreadth below the costal margin. Hemoglobin 7.7 gm., red blood cells 2,400,000. Hematocrit 23 per cent.

Course in Hospital—Roentgenogram showed complete densification of the left hemithorax, with prominent displacement of the mediastinal structures to the right. Two thousand cc. of blood were withdrawn from the left pleural space, and 1000 cc. given in replacement, following which he appeared subjectively improved. The hemoglobin rose first to 10.5 gm. and then to 13 gm. at the end of the first week. Follow-up x-ray films showed little clearing and the mediastinum remained displaced. A circumscribed density was identified in the right mediastinum.

Nine days after admission, he became dyspneic again. The left hemithorax was entered with a trochar, and a large quantity of blood was removed.

On the following day he complained of pain over the right side of the chest, and in 12 hours definite evidence of fluid had appeared. Thoracentesis on the right side yielded 875 cc. of blood. Respiratory distress was marked, and the next day another 1200 cc. were withdrawn. A rubber tube was then inserted on the right side and an additional 1000 cc. drained. In the meantime replacement transfusions totalled 2000 cc. whole blood.

He was transferred to surgery and a left thoracotomy incision was made on October 13. The left pleural space was multiloculated, and the left lower lobe was entrapped in adhesions. At the root, a matted, lobulated lymph node mass measured about 6 x 8 cm. and appeared laden with tumor. Numerous tumor nodules extended posteriorly, and several implants were seen along the parietal pleura. Partial decortication of the left lower lobe was effected and the operative incision closed. Biopsy indicated fibrosarcoma.

He made an uneventful postoperative recovery, but did not gain weight. Because of the noted radioresistance of fibrosarcomas, a trial of triethylenemelamine was elected. He received 1.0 mg. of the drug daily for 10 days without radiographic change in the tumor mass. He died suddenly three weeks later after complaining of back and chest pain.

Pathologic Findings

There was no adenopathy, palpable masses, edema, cyanosis or clubbing. About 2500 cc. of blood was present in each pleural cavity. The blood was loculated by many adhesions. A necrotic mass of neoplastic tissue occupied the middle third of the left chest, adherent to the wall and arising in the mediastinum. The entire mediastinum was shifted markedly to the right. The tumor was reddish-brown in color and quite friable. Little residual lung tissue could be identified, and that remaining was atelectatic. No tumor was seen in the right hemithorax. No extension of tumor outside of the thorax was seen.

Histologically the tumor consisted of streams and whorls of plump spindle shaped cells. Delicate connective tissue fibrils were evident in most fields. The tumor was quite vascular and new capillaries were abundant. Hemorrhage and necrosis were marked in many areas.

The adjacent lung was compressed by the growth of the tumor, but invasion was only superficial. On the other hand invasion of the intercostal muscles and involvement of the periosteum of ribs was prominent.

Acknowledgement: The authors wish to express a debt of gratitude to Dr. Arthur C. Allen for his kind cooperation in reviewing the histological material.

SUMMARY

1. A brief review of the literature on mediastinal tumors is offered, with special attention to fibrosarcoma of the mediastinum.

2. Three unusual cases of mediastinal fibrosarcoma are reported.

3. Two of these showed a remarkable degree of mediastinal compression. Superior vena cava obstruction was extreme and pulmonary insufficiency intractable. Triethylenemelamine had a palliative effect in one case.

4. The third case exhibited bilateral hemothorax and died of exsanguination into the pleural space and mediastinal compression.

SUMARIO

1. Se ofrece una breve revisión de la literatura sobre tumores mediastinales, con especial atención en el fibrosarcoma del mediastino.

2. Se reportan tres casos raros de fibrosarcoma mediastinal.

3. Dos de estos mostraron un grado notable de compresión mediastinal. La obstrucción de una cava superior era extrema y la insuficiencia pulmonar intratable. La Trietilenmelamina tuvo un efecto paliativo en un caso.

4. El tercer caso mostro hemotórax bilateral y murió de exangüinación dentro del especio pleural y compresión mediastinal.

RESUME

1. Les auteurs font une brève revue de la littérature des tumeurs médiastinales en mettant particulièrement en relief le fibrosarcome.

2. Ils rapportent trois cas inhabituels de fibrosarcome du médiastin.

3. Deux d'entre eux entrainèrent un degré important de compression médiastinale. L'obstruction de la veine cave supérieure était énorme et l'insuffisance pulmonaire au-dessus de toute possibilité thérapeutique. Dans un cas, on eu un effet palliatif grâce au triethylenemelamine.

4. Le troisième cas se compliqua d'un hémothorax bilatéral et la mort survint par hémorragie intrapleurale et compression médiastinale.

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Obstructive Emphysema in Pneumonia Simulating Cavity*

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Introduction

The occurrence of obstructive emphysema complicating various forms of pneumonia has been known for many years. Prior to the era of the sulfonamides and the antibiotics large intra-pulmonary bullae and subpleural blebs were frequently noted by pathologists in children dying of pneumonia. Snow and Casassa[1] presented the radiological and clinical picture of this condition in 1937. The occurrence of ring shadows in resolving lobar pneumonia simulating single or multiple lung abscess has also been recorded (Kerley,[4] Pierce and Dirkse,[3] Graeser, Wu and Robertson[2]). A number of authors reported diffuse obstructive emphysema as a prominent pathological finding in influenzal pneumonia during the pandemic of 1918-19 (Wolbach,[5] Torrey and Grosh[6]). For the most part, however, references in the literature to this condition in adults are brief and its importance from the diagnostic and therapeutic standpoint is not amplified. Accordingly it seemed worthwhile to report two cases of localized acute obstructive emphysema or pneumatocele occurring in association with pneumonia and simulating cavitary lung disease.

Case 1: A 59 year old white male garment cutter, was admitted on July 14, 1951, because of hemoptysis. In 1938, 13 years before entry, he had an episode of hemoptysis which lasted for about two days. Two weeks prior to admission he developed a chest cold with cough and purulent expectoration. A chest x-ray film taken then was negative. Symptoms persisted and fluoroscopy by his physician one week before admission is said to have shown a hazy infiltrate in the left infra-clavicular area. He was placed on bed rest at home and two or three days later he suddenly coughed up between a quarter and a half cup of bright red blood. Cough productive of purulent and brownish sputum continued, and a chest x-ray film taken three days before admission, revealed a giant ring shadow surrounded by a zone of hazy infiltration in the left apex and infra-clavicular area. He denied chest pain, fever, chills, weight loss, dyspnea or anorexia.

His family stated that he had been hospitalized at age 18 for pulmonary tuberculosis but he denied this. In 1938, he had an episode of hemoptysis which lasted for about two days. A chest x-ray film was negative at that time.

Physical examination disclosed a patient who was apprehensive, but did not appear to be ill. He appeared older than his stated age. There was impairment of resonance over the left chest posteriorly with a definite area of tubular breathing with bronchophony and increased pectoriloquy approximately six cm. in diameter below and medial to the angle to the scapula. A few post-tussive rales were heard in this area. A grade one aortic systolic murmur was audible over the aortic area, and the aortic second sound was louder than the pulmonic second sound. The blood pressure was 180 systolic, 100 diastolic, pulse rate 100 per minute, respiratory rate 20 per minute and temperature was 98.6° F. The remainder of the physical examination was noncontributory.

Urinalysis revealed a pH of 5.0, specific gravity 1.025, 2+ albumin 1+ sugar and no acetone. There were 2-5 white blood cells, an occasional red-blood cell and no casts in the urinary sediment. Examination of the blood revealed a hemoglobin of 14.2

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grams, red blood cell count 4,500,000, per cubic mm., hematocrit 45 per cent. The sedimentation rate (Wintrobe) ranged between 24 and 32 mm. in one hour. White blood cell count was 13,400 per cubic mm. on admission with 80 per cent polymorphonuclear leucocytes. Four days after admission the white blood cell count was 13,900 per cubic mm. with 70 per cent polymorphonuclear leucocytes and 11 per cent nonsegmented polymorphonuclear neutrophils. The white blood cell count was within normal limits after the 13th hospital day. Fasting blood glucose was 192 mgm., urea nitrogen 23.8 mgm., creatinine 1.4 mgm., per 100 cc. Total protein was 7.0 gm., with albumin of 2.3 grams and globulin of 4.7 gm. per 100 cc. Creatinine clearance was within normal limits. Five sputa and one bronchoscopic specimen were negative for tumor cells on examination by the Papanicolaou method. One bronchoscopic smear, two gastric lavage cultures, and three sputum smears and cultures were negative for tubercle bacilli. An electrocardiogram revealed non-specific changes. Skin tests with blastomycin, coccidioidin and histoplasmin were negative. The tuberculin test was positive using purified protein derivative second strength.

X-ray film inspection of the chest on admission revealed a ring shadow in the left upper lobe measuring 12 cm. in maximum diameter. It extended from the extreme apex to the third anterior interspace (fig. 2). There was a thin zone of infiltration around this ring shadow. A lateral film showed the lesion to lie in the axillary portions of the anterior and apical posterior segments of the upper lobe. There was no evidence of fluid level. Chest x-ray films taken June 25, 1938, and July 2, 1951, 13 *years* and 12 *days* (figure 1) before entry respectively revealed normal lung fields.

He was placed on modified bed rest. The diabetes was readily controlled by means of a diet of carbohydrates 200 gm., protein 150 grams, and fat 100 grams, and thirty units of NPH insulin daily.

On the third hospital day the patient developed pain in the left popliteal region. This was followed in 48 hours by slight swelling and bluish discoloration of the left calf. The lesser saphenous vein was palpable as a cord just below the popliteal space. A diagnosis of thrombophlebitis was made. Signs and symptoms subsided in several days on treatment with bed rest and an elastic bandage. Bronchoscopy on the fifth hospital day revealed only moderate hyperemia of the left upper lobe bronchus. A biopsy taken from deep in the left upper lobe bronchus revealed chronic inflammation in the respiratory mucosa with no evidence of tumor.

On the ninth hospital day he was started on 400,000 units of procaine penicillin G intramuscularly daily. All physical findings had disappeared by the 10th hospital day. Serial x-ray film (fig. 3) revealed progressive decrease in the size of the ring shadow in the left upper lobe and development first of single and then of multiple fluid levels. He was discharged on the 23rd hospital day, but continued aerosol penicillin at home under the direction of his private physician. Chest x-ray films taken six weeks after discharge from the hospital (fig. 4) showed complete resolution of the lesion with only some residual pleural thickening and a linear density in the left

FIGURE 1

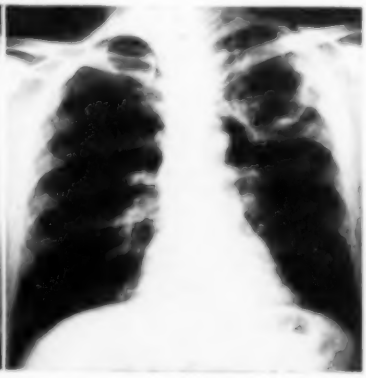

FIGURE 2

Figure 1 (Case 1): Chest roentgenogram taken July 2, 1951, twelve days prior to admission to hospital. There is no evidence of pulmonary infiltration.—*Figure 2* (Case 1): Chest roentgenogram taken July 16, 1951, two days after admission to hospital. There is a ring shadow extending from the left apex to the 3rd left anterior interspace. A moderate amount of parenchymal infiltration and pleural reaction surrounds the lesion.

first anterior interspace. Continued follow-up through October 1953, showed no change in these shadows.

Case 2: A 70 year old white male physician was admitted on August 27, 1951, because of a pulmonary lesion in the right upper lobe. He had been in excellent health until two weeks prior to admission when he developed slight discomfort in the right lateral chest, aggravated slightly by deep inspiration. This was associated with low grade fever. The chest pain subsided within four to five days but the fever persisted. A chest x-ray film was therefore taken and disclosed a ring shadow in the right upper lobe. He was accordingly referred for admission. He denied cough, production of sputum or hemoptysis, and stated that there was no weight loss.

Fifteen years before entry, he had an episode of right sided pleuritis associated with cough and lasting about two weeks. The remainder of the history was non-contributory.

Physical examination revealed him to be in no distress. The chest moved symmetrically and was normally resonant on percussion. Transient crepitant rales and medium and high pitched rhonchi were audible over the right apex posteriorly. The heart was not enlarged on percussion and the aortic second sound was equal to the pulmonic second sound. The rhythm was regular with occasional extrasystoles.

Blood pressure was 150 systolic, 80 diastolic, pulse rate 86, respiratory rate 20 and temperature 99.8° F. rectally.

Urinalysis showed specific gravity of 1.011; no albumin or sugar and 1-3 hyaline and 0-2 finely granular casts per high power field. Examination of the blood showed hemoglobin of 13.8 gm. per 100 cc., red cell count 4,380,000 per cubic mm. hematocrit 45 per cent, 65 per cent polymorphonuclear leucocytes, 10 per cent non-segmenting polymorphonuclears, 2 per cent eosinophiles, 17 per cent lymphocytes and 6 per cent monocytes. The sedimentation rate was 36 mm. in one hour (Wintrobe). Liver profile was within normal limits except for a total protein of 7.65 gms., and albumin of 3.2 gms., and globulin of 4.45 gms. per 100 cc. Kahn test was negative, blood urea nitrogen was 24.7 mgm. and blood glucose was 72 mgm. per 100 cc. Three gastric lavage cultures and one bronchial lavage culture were negative for tubercle bacilli. A bronchoscopic aspiration specimen was negative for secondary organisms, acid-fast bacilli and fungi. Two sputum specimens examined by the Papanicolaou technique were negative for tumor cells. Skin tests with blastomycin, histoplasmin and coccidioidin were negative; tuberculin test was positive to second strength PPD. An electrocardiogram was interpreted as showing non-specific changes.

A chest x-ray film taken three months before admission showed no abnormality of the lungs (figure 5). One taken a few days before admission (fig. 6) disclosed a 5.5 x 4.5 cm. ring shadow in the periphery of the right infraclavicular area. This shadow

FIGURE 3

FIGURE 4

Figure 3 (Case 1): Detail of chest roentgenogram taken on August 2, 1951, the 19th hospital day. The ring shadow is smaller and shows an air-fluid level.—*Figure 4* (Case 1): Detail of chest roentgenogram taken on September 20, 1951. A nodular density in the left 1st interspace is all that remains of the inflammatory process.

was surrounded by a 1 cm. zone of infiltration continuous above with a homogeneous ground glass density in the outer half of the right first anterior interspace. The aorta was slightly tortuous. Fluoroscopic and roentgenographic examination of the chest on admission showed a decrease in the size of the ring shadow to 2 x 4 cm. and resolution of the pulmonary infiltration. The ring shadow was in the posterior segment of the upper lobe. Because of rectal bleeding, barium and air contrast enemas were done and reported negative.

Bronchoscopy one week after admission revealed narrowing of the right lower lobe bronchus to about 5 mm. in diameter. The right upper lobe orifice showed hyperemia most marked on its lateral wall. A biopsy from the right upper lobe bronchus was reported as showing acute and chronic inflammation of respiratory mucosa.

During the period of investigation the only therapy was modified bed rest. On the 13th hospital day he was started on aerosol therapy consisting of 0.3 cc. of 0.25 per cent Neo-synephrine in saline, followed by 50,000 units of penicillin disolved in 1 cc. of saline given four times daily. This medication was continued until discharge on the 30th hospital day. The patient remained afebrile throughout the entire hospital course except during the third week of hospitalization. During the third week the patient developed lowgrade fever in association with superficial thrombophlebitis of the left leg. This followed sigmoidoscopic fulguration of an incidentally discovered benign rectal polyp. He was given anticoagulant therapy with heparin and dicoumarol and recovered uneventfully. Serial fluoroscopy and chest x-ray films (fig. 7) revealed progressive decrease in the size of the ring shadow in the right upper lobe, and clearing of the surrounding pneumonitis. At the time of discharge from the hospital a 2 x 1 cm., ring shadow was still present. An x-ray film taken on November 11, 1951, (fig. 8) five weeks after discharge from hospital revealed complete disappearance of the ring shadow with a residual nodular density in the right infraclavicular area. This remained unchanged in serial x-ray film studies through October 1953.

Discussion

These two patients present a markedly similar clinical picture. Both had an antecedent history of pulmonary disease, one of hemoptysis 13 years before entry, the other of pleurisy 15 years before. Both had negative chest x-ray films taken two weeks and three months, respectively, prior to hospitalization. In both there was a history of acute lower respiratory infection of two weeks' duration with subsidence of most of the symptoms despite the appearance and persistence of a ring shadow in the chest roentgenogram. In both a diagnosis of tuberculosis or lung abscess distal to a

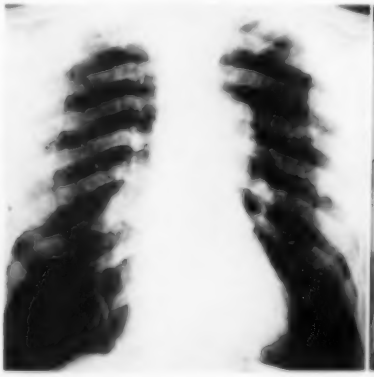

FIGURE 5

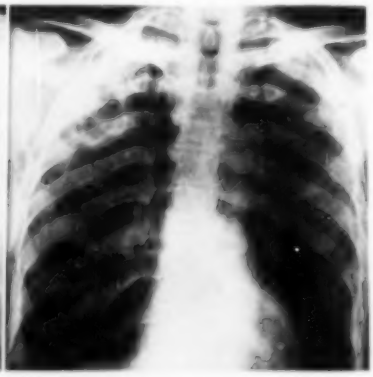

FIGURE 6

Figure 5 (Case 2): Chest roentgenogram taken July 2, 1951, three months prior to hospital admission. There is no evidence of pulmonary infiltration.—*Figure 6* (Case 2): Chest roentgenogram taken August 21, 1951, three days prior to hospital admission. There is a 5 cm. ring shadow in the right infraclavicular area surrounded by a moderate amount of parenchymal and pleural inflammatory reaction.

bronchiogenic carcinoma was seriously considered. These were effectively ruled out. In both there was bronchoscopic and histological evidence of acute and chronic inflammation in the mucous membrane of the bronchus draining the diseased portion of the lung. In case two there was evidence of old bronchial disease in the form of bronchial stenosis of the right lower lobe bronchus. In both, changes in the size of the ring shadows were rapid, although healing of the lesions was not complete for about two months.

Many of the early authors believed that emphysema occurring with pneumonia was on a compensatory basis. Holt, Torrey and Grosh[6] and MacCallum[8] called attention to emphysema and atelectasis in influenzal pneumonia and gave his opinion that they were due to partial or complete bronchial obstruction. It was not, however, until the studies of Jackson, Manges and Spencer[9] in the early 1920's on the changes brought about by aspirated foreign bodies, that a clear understanding of the mechanisms involved was elucidated. Pierce and Dirkse,[7] in 1937, clearly described the development of pulmonary pneumatoceles as a complication of lobar or lobular pneumonia. They ascribed it to a persistent check valve effect in the bronchus due either to non-resolution of the initial inflammation of the bronchus or a subsequent distortion by the dilated airspaces. In only one of the four cases they presented did the pseudocyst disappear, although the surrounding parenchymal infiltration cleared almost completely. They, too, noted the lack of symptoms following the resolution of the initial infection.

It has been our experience that in lobar pneumonias, the bronchial tree is not commonly involved in the infectious process. However, in broncho-

FIGURE 7

FIGURE 8

Figure 7 (Case 2): Detail of chest roentgenogram taken September 17, 1951, on the 20th hospital day. The ring shadow is now much smaller.—*Figure 8* (Case 2): Detail of chest roentgenogram taken November 11, 1951. A linear density at the level of the right 2nd anterior rib is all that remains to mark the site of the original process.

pneumonias of bacterial origin we have been impressed with the high incidence of bronchial inflammation. This bronchitis may be a primary process or may be engrafted on an old bronchial abnormality. Studies on viral pneumonia have also indicated a high incidence of bronchial involvement. The bronchial factor in pneumonia may affect the course and resolution of the infectious process resulting in atelectasis, delayed resolution, pulmonary carnification or obstructive emphysema.

The exact etiology of the pneumonia in our cases is not clear; symptoms subsided in both cases prior to admission, without antibiotic therapy. The absence of any predominant pathogen in the sputum might be taken as pointing to viral pneumonia. Suffice it to say that in both cases there was inflammatory involvement of the bronchial mucosa with congestion and edema. This either alone, or in combination with secretion, produced a check valve effect with entrapment of air beyond the point of obstruction and formation of a pseudocyst. One can only speculate as to why the check valve was formed in the given site. The localization may have been due to old pulmonary disease causing anatomical distortion of the bronchus beyond the limits of bronchoscopic visualization. Or, there may have been a functional abnormality or bronchial cleansing, such as abnormal ciliary action, excessive secretion of rigidity of the bronchial wall. In these cases secondary deformity of the bronchus from the pseudocyst appeared to play little or no part.

There is little exact information available as to the age incidence of this condition. While cases have been reported at all ages, most of them have been in children. This is as might be expected, because of the narrower caliber of the airways in children and the consequent greater ease with which partial obstruction is produced. The occurrence of this condition in these two adult patients may have been related to the known decrease in effectiveness of cough in elderly individuals as well as the possible abnormalities of bronchial function described above.

While the possibility that these lesions were non-putrid lung abscesses cannot be entirely excluded, the early disappearance of symptoms, the small quantity of sputum, the rapid decrease in size of the cyst-like lesions and bronchoscopic findings all militate against it. A similar picture could have resulted from inflammation of the wall of a previously roentgenologically invisible thin walled cyst. Even if this were true, bronchogenic infection and a check valve mechanism must surely have played an important role.

The occurrence of venous thrombosis in the legs of both of these patients raises the question of whether we were dealing with excavation of bland pulmonary infarcts. A review of the literature on this subject discloses differing opinions on the incidence of this complication of pulmonary infarction. Chester and Krause[10] report on 11 instances of abscess formation in 174 subjects with infarcts studied at autopsy. Levin et al[11] report 23 cases of abscess secondary to infarct in 550 necropsies in which pulmonary infarction was a finding. Soucheray and O'Loughlin[12] report the finding of 4 cases of apparent cavitation occurring in serial roentgenograms in a clinical study of 99 cases of pulmonary infarction. None of

their cases were proven pathologically. Cocchi[13] reports infarct cavities occurring 51 times in 385 cases of pulmonary infarction studied at autopsy. The latter author states that the upper portions of the lungs are preferred sites for this complication. The other authors quoted all state that the abscesses have the same distribution in the lungs as uncomplicated infarcts and most commonly involve the lower lung fields. Secondary bronchogenic infection is stressed by all of these authors as the usual cases of secondary infection and subsequent excavation.

In contrast to these reports, Fishberg[14] states that cavity formation due to aseptic necrosis or secondary infection is a very rare complication of pulmonary infarction. Castlemen[15] has stated that secondary infection of a bland pulmonary infarct is a rare coincidence.

Against the diagnosis of cavity in a pulmonary infarct in our cases is the fact that venous thrombosis did not manifest itself until well after hospitalization in both patients. In Case 1 the thrombosis followed a minor surgical procedure on the rectum; in Case 2 the thrombosis was in a superficial vein which only rarely gives rise to pulmonary emboli. The lesions were in the upper lobes in both cases and there was no hemoptysis in Case 2. Finally, on reviewing the literature, we are impressed that this complication of pulmonary infarction has occurred primarily in patients with advanced cardiac disease.

Tuberculosis was dismissed early as the likely diagnosis in the cases here reported, because of the failure to demonstrate acid fast bacilli in the concentrated sputum or in the bronchoscopic smears in the presence of large ring shadows; negative cultures eventually confirmed this approach. Carcinoma was excluded by many negative cytologic examinations of the sputum and bronchoscopic biopsy.

While many of these pneumatoceles will disappear spontaneously with resolution of the bronchial lesion, the course can be hastened and the development of occasional permanent cysts can be prevented by vigorous therapy of the bronchial inflammation. In addition to systemically administered antibiotics, they should be given by inhalation as an aerosol. This is a much more effective way of reaching superficial infection engrafted upon edematous engorged bronchial mucosa.[16] Bronchodilator and vasoconstrictor drugs such as phenylephrine hydrochloride or nor-isopropyl epinephrine should also be used by the inhalation route. In some instances aminophylline or other bronchodilator drugs should be given systemically. Expectorants, carbon dioxide and steam inhalations for thinning secretion also have a place in selected cases.

SUMMARY

Localized obstructive emphysema complicating pneumonia and resulting in pseudocysts or pneumatoceles is reported in two male adults. The literature is reviewed and the differential diagnosis discussed. The role of partial bronchial obstruction in producing the condition and the importance of directing therapy to the diseased bronchus are emphasized.

SUMARIO

Se reportan dos casos de neumonía en hombres adultos complicada con enfisema localizado obstructivo que evolucionaron a pseudoquistes o neumatoceles. Se revisa la literatura y se discute el diagnóstico diferencial. Se hace énfasis en el papel de la obstrucción bronquial parcial como causa del padecimiento y la importancia de dirigir la terapéutica al bronquio enfermo.

RESUME

Les auteurs rapportent deux observations d'adultes du sexe masculin qui, à la suite d'une pneumonie, furent atteints d'emphysème obstructif localisé, ce qui amena la formation de pseudokystes ou de pneumatocèles. Ils donnent à cette occasion une revue de la littérature et discutent le diagnostic différentiel. Ils insistent sur l'action d'une obstruction bronchique partielle dans de tels cas, et sur l'importance d'un traitement directement appliqué sur la bronche atteinte.

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A Study of the Neurotoxicity of Streptoduocin on Tuberculous Patients*

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The ototoxic effect of the streptomycin drugs, particularly when administered over prolonged periods as in the treatment of tuberculosis is well known. Both laboratory[1, 2, 3] and clinical studies[4] have demonstrated that streptomycin predominantly produces vestibular dysfunction and dihydrostreptomycin, auditory impairment. To avoid or minimize these ototoxic effects of streptomycin and dihydrostreptomycin, a mixture consisting of streptomycin and half dihydrostreptomycin—known now as streptoduocin—was suggested (Dr. L. B. Hobson), on the theoretical basis that halving the dose of each drug should greatly reduce the toxic effect of each and yet produce a combined therapeutic effect. Studies with laboratory animals receiving streptoduocin did indeed indicate it to be less toxic than streptomycin for the vestibular apparatus.[1, 2] The California investigators[5, 6, 7] and the Sita—Lumsden[8] group, as well as our own,[9] have since demonstrated clinically that streptoduocin is less toxic than equivalent doses of either streptomycin or dihydrostreptomycin for the auditory and vestibular functions. The present paper includes our further studies with streptoduocin with comparison of seven different regimes of therapy:

1) Patients receiving daily streptomycin and isoniazid (INH) or para aminosalicylic acid (PAS).
2) Patients receiving twice weekly streptomycin and INH or PAS.
3) Patients receiving daily dihydrostreptomycin and INH or PAS.
4) Patients receiving twice weekly dihydrostreptomcin and INH or PAS.
5) Patients receiving daily streptomycin and INH or PAS.
6) Patients receiving twice weekly streptoduocin and INH or PAS.
7) Patients receiving twice weekly streptoduocin, who had shown toxic reactions to the 8th nerve with streptomycin or dihydrostreptomycin.

The first four categories have been extensively studied and reported elsewhere—we wish to report our results in the latter three groups, using the first four as controls.

A group of 272 patients, with moderately or far advanced pulmonary tuberculosis (having about 5 per cent extra pulmonary tuberculosis, either renal or gastro-intestinal), and an equal number as a control group, who had no previous therapy with either streptomycin or dihydrostreptomycin, were put on a regime of one gram of streptoduocin and usual dosage of isonicotinic acid hydrazide (200 mgms daily) or para-aminosalicylic acid (PAS) 12 grams daily. One (136 patients) part of the study involved

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daily therapy for four months, while another (136 patients) group received twice weekly therapy for eight months.

In the streptoduocin group—after four months of daily therapy there was no neurotoxicity (either nerve or vestibular) compared to 30 per cent vestibular damage with streptomycin and 26 per cent impaired hearing with dihydrostreptomycin. After four months of twice weekly treatment, (at present the most accepted therapy in pulmonary tuberculosis) there was no vestibular nor cochlear damage in any of the 136 patients receiving streptoduocin—compared to 5 per cent vestibular damage with streptomycin and 4 per cent cochlear injury with dihydrostreptomycin, in an equal number of controls.

After eight months of twice weekly injections of streptoduocin in a group of 106 patients, only one showed evidence of mild vestibular damage with none showing cochlear injury. In an equal number receiving twice weekly injections of streptomycin, 6 per cent had vestibular disturbance and 0.5 per cent cochlear injury. A similar group, receiving dihydrostreptomycin twice weekly for eight months, revealed 1 per cent had vestibular damage and 6 per cent had cochlear damage. The clinical response was similar with all three regimes of treatment, but the toxic effects were practically eliminated using streptoduocin.

There were 21 patients admitted to our hospitals, who had received 2 or 3 grams, daily, of streptomycin or dihydrostreptomycin, for three to eight weeks (by outside physicians). On admission, these patients showed marked evidence of vestibular disturbance and/or marked deafness. All specific drug therapy was discontinued for one to two weeks, with some improvement in the vestibular and cochlear functions. Then streptoduocin was given twice weekly, supplemented with usual doses of INH or PAS. Therapy has now been continued for three to eight months with continued improvement in vestibular function and slight improvement in deafness. The clinical results were similar to those found in other studies, that is, improvement (symptomatic and/or objective) in about 50-60 per cent of moderately and far advanced cases of pulmonary tuberculosis. Improvement was measured by changes in cavity size, sputum conversion, blood studies, etc.

Our last study group of 24 patients, who had received 1 gram of streptomycin or dihydrostreptomycin daily for 30 to 60 days, showed signs of vestibular and/or cochlear toxicity—an unusually susceptible group to eighth nerve damage. They were given a rest period from specific therapy of one to two weeks, with improvement in eighth nerve function. At this time streptoduocin was started—with no further increase in toxicity—in fact, vestibular function continued to improve, returning to normal, and slight cochlear improvement was found. The usual beneficial clinical results continued.

The vestibular and cochlear evaluations were both clinical findings and specific labyrinth and audiometric studies by our otologist (Dr. Rutberg). Vestibular function was studied by the cold caloric test, with water at 68° F. flushed to the ear drum—individually testing the vertical and hori-

136 Patients Four months	Vestibular Damage Daily Therapy	Vestibular Damage Twice Weekly	Cochlear Damage Daily Therapy	Cochlear Damage Twice Weekly
	per cent	per cent	per cent	per cent
Streptomycin	30	5	6	0.5
Dihydrostreptomycin	5	1	26	4
Streptoduocin	0	0	0	0

106 Patients Eight months	Vestibular Damage Twice Weekly	Cochlear Damage Twice Weekly
Streptomycin	6 per cent	0.5 per cent
Dihydrostreptomycin	1	6
Streptoduocin	1	0

zontal canals by tilting the head. Normally in 30-50 seconds, a rotary nystagmus appears with the major component to the opposite side. Toxic patients showed delayed or no response. Both the time of reaction and amplitude of nystagmus were measured. This was followed by the Rinne test to differentiate obstructive deafness, by comparing air and bone conduction, which normally is 2:1. Repeated audiograms were made on streptoduocin and control patients—with normal range, depending on age, considered from 20 to 30 decibel level for higher tones.

This study was aided by a grant from E. R. Squibb and Sons, who also supplied the Distrycin (streptoduocin). We wish to thank Drs. L. H. Hobson and John Groel for their co-operation and assistance.

CONCLUSIONS

The value of the streptomycin group of drugs as the therapy of choice in the treatment of tuberculosis has been well established, in combination with INH and/or PAS. The toxic effects on the vestibular and cochlear organs have somewhat restricted its use and limited it's effectiveness. The incidence of toxicity of streptomycin or dihydrostreptomycin in our study is greatest during the first four months of therapy—most marked when given daily, but still showing definite toxicity even when give twice weekly. A mixture of equal parts, that is 0.5 gram streptomycin and dihydrostreptomycin—recently given the generic name of streptoduocin, by the American Medical Association, Council of Pharmacy and Chemistry, almost completely eliminated these toxic effects, without affecting their clinical value. As a result of this study, it is our feeling that streptoduocin, should be used almost exclusively, with usual supplemental drugs, instead of either streptomycin or dihydrostreptomycin. These studies are being continued and further reports will be made.

RESUMEN

El valor del grupo de drogas de la estreptomicina como tratamiento de elección se ha establecido bien, en combinación con INH y/o PAS.

Los efectos sobre los órganos vestibulares y cocleares han restringido un poco su uso y han limitado su efectividad. La incidencia de la toxicidad de la estreptomicina y de la dihidroestreptomicina en nuestro estudio es la más grande durante los primeros cuatro meses de tratamiento, más marcada cuando se administran a diario pero aún hay toxicidad-cuando se administran dos veces por semana. Una mezcla de partes iguales de estreptomicina y dihidroestreptomicina (0.5 gm. de cada una) recientemente nombrada Estreptoduocina, por el Consejo de Química y Farmacia de la

A.M.A., eliminó casi completamento los efectos tóxicos sinafectar el valor clínico. Como resultado de este estudio es nuestra impresión que la estreptoduocina debe ser empleada casi exclusivamente, con las drogas suplementarias habituales, en lugar de la SM o la DHSM.

Estos estudios se continúan y se harán comunicaciones relativas en el futuro.

RESUME

Pour le traitement de la tuberculose, la valeur de la streptomycine, associée à l'isoniazide et au P.A.S. ou à l'un de ces produits, a été parfaitement établie. Les effets toxiques sur les fibres vestibulaires et cochléaires ont dans une certaine mesure apporté une restriction à l'utilisation de l'antibiotique, et ont limité l'importance de son action. Au cours de leur étude, les auteurs ont remarqué que les accidents toxiques de la streptomycine ou de la dihydrostreptomycine sont plus importants au cours des quatre premiers mois du traitement. Ils sont plus nets lorsque le produit est administré quotidiennement, mais peuvent entraîner des effets toxiques incontestables, même lorsqu'ils sont administrés seulement deux fois par semaine. Un mélange à parties égales de 50 cgr. de streptomycine, et de dihydrostreptomycine, que récemment laCommissio n de Pharmacie et de Chimie de l'American Medical Association a baptisé du nom de "streptoduocine," a permis d'éliminer presque complètement ces effets toxiques sans diminuer la valeur thérapeutique du produit.

En conclusion de leur travail, les auteurs pensent que la "streptoduocine" devrait être utilisée d'une façon à peu près exclusive, associée aux autres produits habituels, au lieu d'utiliser soit la streptomycine, soit la dihydrostreptomycine. Les auteurs continuent leurs travaux et pensent apporter ultérieurement de nouvelles conclusions.

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Case Report Section

Isolation of Avian Tubercle Bacilli in Human Silicosis

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Infection with Mycobacterium avium is common among poultry in many parts of the United States; such infection is also known to occur in swine and cattle.[1] However, as far as we are able to determine, the isolation and unequivocal identification of avian tubercle bacilli from a human source have been recorded only once in this country.[2] In the world literature available to us there are reports of approximately 25 cases in which the avian tubercle bacillus has been isolated from human sources and has been adequately identified, although infection of chickens, swine and cattle is known to exist in many countries.*

This report is made not only because it is unusual to find avian tubercle bacilli in material from human sources but also because evidence exists that the patient had silicosis. This is of special interest in view of the demonstration that relatively avirulent variants of tubercle bacilli may proliferate in experimental silicotic lesions of guinea pigs.[7-9]

Report of Case†

A 59-year-old white man was referred to the Mayo Clinic in October, 1950, because of increasing respiratory difficulty. Symptoms of pulmonary distress and edema of the lower extremities were so severe that he was hospitalized on arrival. Five years prior to admission the patient had started to work as a tool grinder. Two years later he had been hospitalized for pneumonia and pleurisy with effusion, and 500 ml. of fluid was withdrawn from the left pleural space. At that time he had been told his lungs were probably "dusted." He had continued to work but had experienced periodic episodes of respiratory distress. A year prior to admission he had had "asthma" and shortness of breath and had been unable to work for about 6 weeks. At times it had been necessary to sleep supported by several pillows. In spite of this he had continued in his occupation until 2 weeks prior to admission, when dyspnea on the slightest exertion and edema of his legs forced him to rest.

Examination at the clinic revealed rales in each lung and edema of the feet, ankles and lower portions of the legs. A roentgenogram of the thorax revealed multiple patchy areas of infiltration in both lungs, a small amount of fluid in each pleural space and evidence of fibrosis in both bases (fig. 1). Review of the roentgenograms made elsewhere indicated a slight but definite progression of the pulmonary lesions for the past 3 years. A tuberculin test using 0.005 mg. of PPD gave no reaction. Microscopic examination of sputum failed to disclose acid-fast bacilli. Three specimens of sputum and two gastric washings were obtainable for culture of acid-fast bacilli.

A diagnosis of silicosis with cor pulmonale was made. The patient was treated with digitoxin and a diet containing 0.5 gm. of sodium. Great improvement took place; he lost 25 pounds of fluid in 7 days, and after 11 days of hospitalization he was dismissed. He returned home, where he died 2 weeks later of cardiac failure.

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*Reviews of the reports on human infection with avian tubercle bacilli have been made by Feldman,[1, 3, 4] Rich[5] and Fontana.[6]

†This case has been briefly mentioned in a previously published abstract.[10]

Necropsy* disclosed chronic passive congestion of the lungs, liver and spleen. Adhesive pericarditis and bilateral pleuritis were noted. The lungs were severely anthracotic and several small cavities were adjacent to the anthracotic zones.

Microscopically, the anthracotic regions consisted of dense hyalinizing connective tissue with masses of pigment (fig. 2*a*). A few small foci of necrosis were present that contained a few acid-fast bacilli but the histopathologic picture was not typical of tuberculosis. When sections of pulmonary tissue were examined with polarized light, many collections of birefringent crystals resembling silica were seen (fig. 2*b*). Unfortunately, no material was available for study by incineration.

Bacteriologic Examination

Cultures for acid-fast bacilli were made on 5 successive days, using the aforementioned three specimens of sputum and two gastric washings. Four tubes of modified Löwenstein-Jensen medium were used for each specimen. As already indicated, no acid-fast bacilli were found in smears of the sputum; smears of the gastric contents were not made.

Colonies of acid-fast bacilli were obtained from each of the first four specimens, as shown in the table. The colonies were small, round, glistening and slightly yellowish or buff colored, which was recognized to be typical of avian tubercle bacilli. All the colonies on each tube in the successive isolations were identical in appearance. Organisms obtained on culture from one specimen were selected for tests of pathogenicity for chickens, rabbits and guinea pigs, and for *in vitro* tests of sensitivity to

FIGURE 1: Roentgenogram at the time of admission showing patchy areas of infiltration and bilateral pleural effusion.

*We are indebted to Dr. D. G. Henderson, Director of Laboratories, Aultman Hospital, Canton, Ohio, for providing us with a report of the necropsy and for permission to examine histologic preparations.

Results of Cultures for Acid-fast Bacilli on 5 Successive Days

Specimen	Smear for acid-fast bacilli	Material	Results of culture*
1	Negative	Sputum	1 colony on 1 tube
2	Negative	Sputum	10 colonies per tube
3	Not done	Gastric washing	4 colonies per tube
4	Negative	Sputum	5 colonies per tube
5	Not done	Gastric washing	No growth in 8 weeks

*Average number of colonies per tube.

drugs. Organisms grown from another specimen were subsequently used to repeat the tests for pathogenicity in animals.

Pathogenicity in Animals.—For the inoculation of animals, several colonies from the original culture were suspended in sterile water by rubbing a loopful of growth on the inside of the test tube. A uniform and stable suspension was readily formed, which is characteristic of avian tubercle bacilli. This suspension was diluted with sterile water to a density of one tenth that of tube no. 1 of McFarland's nephelometer. A portion of this suspension also was used to inoculate medium for in vitro tests for sensitivity to drugs as described later.

Two chickens, approximately 1 year old, were obtained from a flock known to have been free of avian tuberculosis for at least 2 years. They failed to react to either avian tuberculin or old tuberculin (OT) when

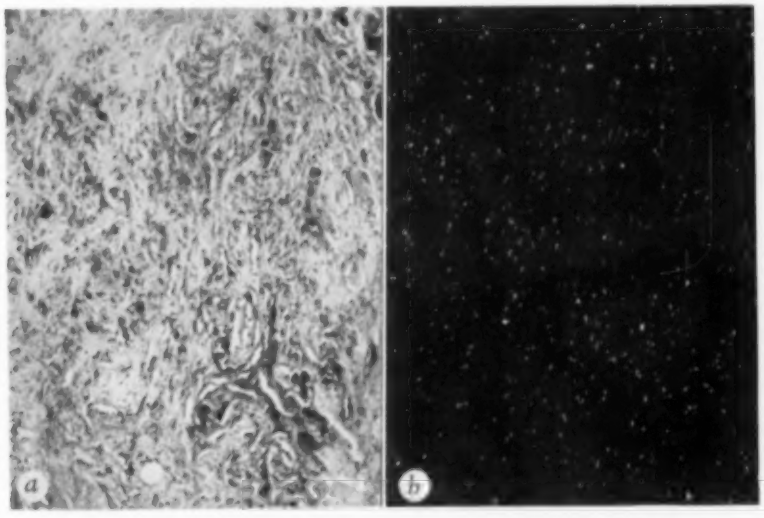

FIGURE 2A FIGURE 2B

Figure 2a: Section of lung showing dense fibrous areas with collections of black pigment. A few small necrotic foci contained a few acid-fast bacilli (hematoxylin and carbolfuchsin; × 100. *b:* Picture of same section taken with polarized light to show the birefringent crystals typical of silica (× 100).

tested 4 days prior to inoculation. Each received an intravenous injection of 1 ml. of the suspension. Each of two mature rabbits was given 1 ml. intravenously. Two guinea pigs received similar doses injected subcutaneously over the sternum.

The chickens died on the thirty-ninth and forty-first day respectively. In each, the spleen was about 10 times the normal size, the liver was enlarged and yellowish in color, and the kidneys were enlarged and congested. Smears from the spleen, liver and femoral marrow disclosed innumerable acid-fast bacilli. The rabbits died on the seventeenth and eighteenth day respectively, and each had enlargement of the spleen (six to eight times) and pulmonary congestion. Smears from the spleen showed innumerable acid-fast bacilli. The guinea pigs were tested on the eighty-sixth day with 0.1 ml. of a 1:100 dilution of OT and with avian tuberculin. The reaction to OT consisted of a firm erythematous zone about 6 mm. in diameter, whereas the reaction to avian tuberculin was a raised erythematous zone 25 mm. in diameter. When the guinea pigs were killed on the ninetieth day of infection, a small caseous lesion about 5 mm. in diameter was found in each at the site of injection, along with necrosis of an axillary lymph node. All other organs were grossly normal.

Histopathologic examination of various organs from the rabbits and chickens disclosed widespread tuberculous lesions containing large numbers of acid-fast bacilli. The organs of the guinea pigs were microscopically normal except for the sites of inoculation and the axillary lymph nodes, which presented circumscribed necrotic processes with many acid-fast bacilli. Cultures were made from the spleens of the chickens and rabbits and the site of inoculation of one guinea pig; colonies typical of avian tubercle bacilli eventually appeared in all. Organisms obtained on culture from the spleen of a rabbit produced fatal disease in two chickens and two rabbits but failed to cause any lesions in the internal organs of two guinea pigs.

The tests for pathogenicity in animals were repeated, using another of the original cultures from this patient. The procedures were the same as in the series just described. The rabbits died on the seventeenth and twenty-fourth day respectively, and the chickens died on the twenty-eighth and fifty-fourth day. The latter chicken was tested on the thirty-fifth day with 0.1 ml. of a 1:100 dilution of OT and 0.1 ml. of avian tuberculin, each given intracutaneously in a wattle. There was no reaction to the OT, whereas a 4+ reaction was recorded for the test with avian tuberculin. Smears from the enlarged spleens of the rabbits and chickens contained innumerable acid-fast bacilli.

The guinea pigs were tested on the thirty-fifth day with avian tuberculin and with OT as described for the first series. Only a slight reaction occurred to OT but the test with avian tuberculin produced a 4+ reaction with necrosis. The tuberculin tests were repeated on the seventy-fourth day. The tests with OT resulted in a slight reaction in one guinea pig and a doubtful reaction in the other. The avian tuberculin, however, caused erythematous raised zones 20 mm. in diameter, with necrosis at the centers.

In Vitro Sensitivity Tests.—A portion of the suspension used to inoculate the first series of animals was inoculated on three series of egg-yolk agar medium containing streptomycin, para-aminosalicylic acid and isoniazid respectively. It was found that the microorganisms were resistant to 10 but not to 50 micrograms of streptomycin, to more than 10 micrograms of para-aminosalicylic acid and to more than 40 micrograms of isoniazid per milliliter respectively. This relative resistance is characteristic of avian tubercle bacilli.

Comment

As already mentioned, although no material was available for incineration, examination of sections by polarized light did reveal innumerable birefringent crystals characteristic of silica. The diagnosis of silicosis is substantiated by the history, the roentgenographic appearance, the signs of cor pulmonale and the histopathologic appearance of the pulmonary lesions. We believe that the finding of avian tubercle bacilli is incidental and that these microorganisms played little part, if any, in the pulmonary fibrosis. It may be that the silicotic lesions provided a more favorable medium for growth of the avian tubercle bacilli, which normally are relatively avirulent for man. This suggestion is made in view of the aforementioned finding that avirulent variants of tubercle bacilli may proliferate in experimental silicosis in guinea pigs but fail to become established in normal guinea pigs.[7,9] We have been unable to learn anything of the patient's history with respect to the source of the microorganism. It is of interest to note that his home was in a rural community in that part of the United States where tuberculosis among chickens is most prevalent[1].

Infection with the avian tubercle bacillus is so rarely reported in man that skepticism regarding its occurrence is justifiable. We agree with Rich[5] that in the majority of reports the identification of avian tubercle bacilli is incomplete or is such as to cast doubt on the validity of the claim. We also agree with Rich that proof of the identity of avian tubercle bacilli must rest on pathogenicity for rabbits and chickens and failure of the microorganism to produce progressive disease in guinea pigs. In our case, these criteria have been met in each of two cultures isolated from the patient on different days. The animal inoculations were made with original cultures. The isolations were made in a laboratory where avian tubercle bacilli were not being handled.

SUMMARY

Acid-fast microorganisms with the cultural characteristics of avian tubercle bacilli were isolated from three specimens of sputum and a gastric washing from a patient with silicosis. These organisms were virulent for chickens and rabbits but failed to produce progressive disease in guinea pigs. The infected animals reacted slightly to old tuberculin but severely to avian tuberculin. Additional studies on one culture revealed it to be resistant in vitro to streptomycin, para-aminosalicylic acid and isoniazid, which is typical of avian tubercle bacilli.

The patient died of cardiac failure. Sections of lung revealed extensive pneumonoconiosis and fibrosis. Birefringent crystals typical of silica were seen in sections examined with polarized light. It is believed that the avian tubercle bacilli played little part, if any, in the production of pulmonary fibrosis and that these microorganisms were able to proliferate because of the pre-existing silicotic lesions in a host for which avian tubercle bacilli are normally relatively avirulent.

RESUMEN

Se aislaron microorganismos ácido-resistentes con las características de cultivo del germen aviario, de tres muestras de esputos y lavado gástrico de un enfermo de silicosis. Estos organismos fueron virulentos para las gallinas y los conejos pero no produjeron enfermedad progresiva en los cuyes. Los animales infectados reaccionaron ligeramente a la tuberculina antigua pero severamente a la tuberculina aviaria. Los estudios adicionales de un cultivo revelaron que era resistente in vitro a la estreptomicina, al ácido paraminosalicílico y a la isoniacida, lo cual es típico del bacilo aviario.

El enfermo falleció de insuficiencia cardiaca. Las secciones del pulmón revelaron extensa neumoconiosis y fibrosis. Se encontraron cristales birrefringentes típicos de sílice en las secciones examinadas con luz polarizada. Se cree que el bacilo aviario desempeñó muy pequeño papel, si acaso alguno, en la producción de la fibrosis pulmonar y que estos microorganismos fueron capaces de proliferar a causa de las lesiones silicosas preexistentes en un huésped para el cual aviario es, normalmente, avirulento.

RESUME

Des micro-organismes acido-résistants ayant les caractères de culture des bacilles tuberculeux aviaires ont été isolés à partir de trois produits d'expectoration et de lavage gastrique chez un malade atteint de silicose. Ces microbes étaient virulents pour les poulets et les lapins, mais ne réalisèrent aucune affection évolutive chez les cobayes. Les animaux infectés réagirent faiblement à la tuberculine brute de Koch, et fortement à la tuberculine aviaire. Les études ultérieures d'une culture montrèrent que le bacille était résistant in vitro à la streptomycine, au P.A.S. et à l'isoniazide, ce qui est caractéristique du bacille tuberculeux aviaire.

Le malade mourut d'insuffisance cardiaque. Des coupes du poumon montrèrent une pneumoconiose extensive et une fibrose. Des cristaux biréfringents de silice furent notés sur les coupes examinées à la lumière polarisante. Les auteurs pensent que le bacille aviaire ne joua qu'un faible rôle, si toutefois il en joua un, dans la production de fibrose pulmonaire. Pour eux ce sont les lésions silicotiques préexistantes qui permirent la végétabilité de ces bacilles.

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Trends in Tuberculosis Therapy

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The following case of pulmonary tuberculosis is reported because of its unusual features. In one person are encountered most of the current medical and surgical procedures as they have appeared over the past 10 years. This patient is still alive and well because of the propitious appearance of chemotherapeutic and antibiotic aids, with advances in thoracic surgery. The striking transition in the treatment of tuberculosis plus its various pitfalls and complications are demonstrated.

This is the history of a 36 year old woman who contracted her disease in 1942 at the age of 25, 20 months after the birth of her only child.[1] There was no known contact or family history. An x-ray film taken at the onset of symptoms of cough, pleurisy and fever revealed minimal pulmonary tuberculosis. On being checked five months later at the local health unit, this had spread to far advanced bilateral disease. On May 1943, she entered the sanatorium.* Pneumothorax and bed rest was then the accepted treatment for fresh exudative progressive disease. Following negative bronchoscopy, artificial pneumothorax was instituted, first on the right and then on the left. She responded well, and in October 1944, after a year and a half of treatment, was discharged with the advice to maintain the bilateral collapse. A year later, in 1945, a large right pleural effusion appeared accompanied by fever and dyspnoea. Despite thoracentesis the fluid re-accumulated and it was necessary to abandon both the right

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and left pneumothorax. The collapse of the right lung had been maintained for two years and four months, the left for two years. Because of elevated temperature she re-entered the sanatorium where, after a few months of bed rest, her sputum turned positive and a cavity appeared at the left apex (March 1946).

Pneumoperitoneum, which was then becoming popularized, was instituted in April 1946 followed in a few months by left phrenic crush. Her first extra-pulmonary complication, a tuberculous fistula-in-ano developed, and responded to surgical treatment. In May 1947, as the right side appeared stable, left first stage thoracoplasty was performed in an attempt to close the cavity still present in the left upper lobe. Marked dyspnoea

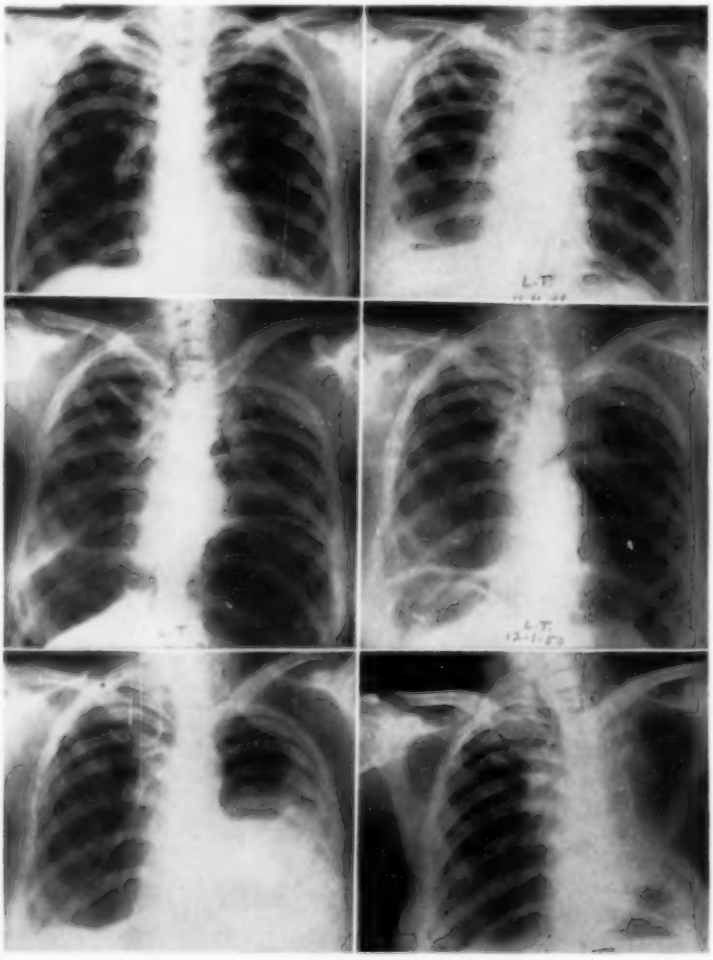

FIGURE 1

and tachycardia followed the operation and it was deemed unwise to proceed with further stages.

Following surgery, the sputum was no longer positive. A laminogram, however, six months after the operation, revealed a small cavity at the left apex beneath the thoracoplasty. Despite this finding, it was decided that in view of her inability to undergo further surgery to discharge her home. Therefore she left the sanatorium in December 1947, pneumoperitoneum being maintained. She did well for a year when a slight spread appeared at the left base. This cleared after a month of bed rest but reappeared five months later in May 1949 along with positive sputum.

Streptomycin was given for the first time and continued for 32 consecutive days with conversion of sputum to negative. In August 1949 another spread appeared at the left apex necessitating re-entry to the sanatorium for the third time. A second course of 30 doses of streptomycin with para-aminosalicylic acid (PAS) was started September 1949. Pneumoperitoneum was continued. However she did poorly and her sputum remained positive. Tuberculous bronchitis was now (Feb. 1950) revealed

CHART I

Sanatorium Admission	Collapse Treatment	Drug Treatment	Surgery & Procedures	Complications
I. May '43- Oct. '44	Rt. Pneumothorax June '43- Oct. '45		Bronchoscopy Oct. '43	
	Left Pneumothorax Oct. '43- Oct. '45			Left Pleural Effusion 1945
				Fistula-in-ano 1946
II. Dec. '45- Dec. '47	Left Phrenic Crush July '46 and July '47	SMC: April-May '49 (32)	1st Stage Thoracoplasty May '47	Empyema & Broncho-Pleural Fistula April '51
	Pneumoperitoneum April '46 Feb. '51	SMC & PAS: Sept.-Oct. '49 (30) Tibione: Mar.-April '50	Bronchoscopy Feb. '50	Transfusion Reaction May '52
		SMC & PAS: May-Nov. '50 (177) SMC & PAS: June '51-Mar. '52 (173)		Inguinal Abscess Nov. '52
III. Oct. '49- Dec. '52		Nov.-Dec. '52 (15)	Left Pneumonectomy Feb. '51	Serum Hepatitis Feb. '53
		Isoniazid 200 mgm March '52-present	Left Schede Thoracoplasty May & July '52 (2 stages)	

Pulmonary Function Tests April 1950:
MBC 35 L/min. (35 per cent predicted)
Vital Capacity 1,170 (38 per cent predicted)
Left Lung contributes 1/3 Total Function

Total Streptomycin Dosage: 429 Grams

by bronchoscopy. Tibione became available at this point but after one month on the drug, it was stopped because of nausea, vomiting, and 10 per cent bromesulfalein retention.

In May 1950 a third course of streptomycin was instituted in conjunction with PAS. The antibiotic was given daily for 131 doses, then biweekly, for a total of 177 grams, ending in November 1950. In April 1950 pulmonary function tests and bronchospirometry were done which revealed a maximum breathing capacity of 35 per cent of predicted, with the left lung contributing only one third of the total. Because of this further surgery was deemed inadvisable. Following these tests however, her condition worsened and the cavity enlarged. As a dsperate measure, left pneumonectomy was performed February 1951 despite the function tests. The postoperative course was stormy as anticipated. She seemed to do well for two months when empyema and broncho-pleural fistula developed. A fourth course of streptomycin and PAS was given June 1951 and continued biweekly until March 1952, for a total of 173 grams. Streptomycin lost its effect about February 1952, when daily fever appeared and her condition deteriorated clinically. Reactivity was now present at the right apex. Surgery was necessary but she was too ill. Isoniazid became available at this time and was started March 1952. The response was dramatic. Her temperature dropped to normal in 10 days and in two months she underwent the first of two Schede operations on the left for the purpose of closing the empyema space. Following the first Schede, a transfusion reaction occurred, associated with anuria for two days, but this slowly resolved without apparent permanent kidney damage. November 1952 another extra pulmonary complication appeared; an inguinal abscess which required incision and drainage. This apparently involved the deep inguinal glands which broke down. It proved to be a sterile abscess and the wound was closed and healed completely in one week. A fifth course of streptomycin and PAS was given in November and December of 1952 for a total of 15 grams, along with isoniazid. However the streptomycin and PAS were stopped in December and only isoniazid, 200 mgm. daily, has been maintained to the present. She was discharged home from the sanatorium in December 1952. In February 1953, hepatitis, probably of serum type, appeared. This was moderately severe but had cleared by early April 1953.

Clinically this woman is comfortable and can carry out simple household duties but exertion causes dyspnoea and tachycardia. There is no cough or expectoration and gastric cultures are now negative. Her resting pulse is 100 to 120.

Acknowledgement: I wish to thank Dr. Theodore L. Badger for his valuable suggestions in the preparation of this paper.

CONCLUSIONS

This illustrates the great strides that have occurred in tuberculosis therapy. Today one would not consider pneumothorax for her original lesion but would treat it with intermittent streptomycin in conjunction with PAS or isoniazid. Streptomycin is no longer used alone as it was

originally given to this patient, leading to bacterial resistance. It is also of interest that her pulmonary function tests showed a maximum breathing capacity of 35 litres per minute or 35 per cent of the predicted and a vital capacity of 1,170 or 38 per cent of predicted. Nevertheless she was able to undergo left pneumonectomy and subsequent surgery on the chest wall. This illustrates that adverse results in pulmonary functions tests *per se* need not preclude life-saving surgery to a desperate case.

CONCLUSIONES

Este caso ilustra los grandes cambios que han ocurrido en la terapéutica de la tuberculosis. Hoy no se consideraría el neumotórax para la lesión original de esta enferma, sino que se trataría con estreptomicina intermitente en conjunto con el PAS o isoniacida. Ya no seusa más la estreptomicina sola como era originalmente administrada a este tipo de paciente, llevando a la resistencia bacteriana. Es de interés también, que sus pruebas de función pulmonar mostraron un máximo de capacidad respiratoria de treinta y cinco litros por minuto o 35 por ciento de lo predicho y una capacidad vital de 1170 o 38 por ciento de lo predicho. De toda maneras la paciente pudo soportar una neumonectomía izquierda y cirugía de la pared torácica subsecuentemente. Esto ilustra que los resultados adversos en las pruebas de las funciones pulmonares no precluyen en un caso desesperado la cirugía para salvar la vida del paciente.

RESUME

Le cas publié illustre les progrès qui sont survenus dans la thérapeutique de la tuberculose. Aujourd'hui pour une telle malade, on ne devrait pas envisager le pneumothorax pour traiter une lésion à son début, mais on devrait utiliser la streptomycine intermittente en association avec le P.A.S. ou l'isoniazide. La streptomycine n'est plus utilisée seule, comme elle le fut au début chez cette malade, entrainant la résistance des bacilles. Il est également intéressant de noter que les examens de sa fonction pulmonaire montrèrent une capacité respiratoire maximum de 35 litres par minute, ou 35% de la normale, et une capacité vitale de 1,170 litre, ou 38% de la normale.

Néanmoins, elle fut capable de supporter une pneumonectomie gauche et ensuite une intervention chirurgicale sur la paroi thoracique. Ceci montre que das résultats défavorables des examens fonctionnels, si on les considère intrin sèquement, ne s'opposent pas forcément à une chirurgie de sauvetage dans un cas désespéré.

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Hepatitis Following Isoniazid

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A review of the literature reveals but one case of toxic hepatitis with jaundice resulting from isoniazid. In 1953 Randolph and Joseph[1] reported the first case of toxic hepatitis with jaundice in a patient treated with isoniazid. Toxic effects to the liver are rare in clinical experience as evidenced by normal liver function tests with the use of this drug. Selikoff and Robitzek[2] found this to be their experience. Isoniazid is now in much wider use in the treatment of tuberculosis and evidences of toxicity merit reporting.

V. N., a 30 year old white male was admitted to the Veterans Administration Hospital, Tucson, Arizona on November 16, 1953 for the treatment of pulmonary tuberculosis. The diagnosis was first established in 1944 and treatment had not included antimicrobial drugs prior to the present admission. He was considered inactive from 1946 until a positive culture of the sputum was obtained in September 1953 and he was advised to be hospitalized.

Physical examination on admission revealed a well nourished white male who appeared neither acutely or chronically ill. Temperature was 98.6° F., pulse 82, blood pressure 120/70, weight 158 pounds. Complete physical examination was normal except for the lungs which revealed restriction of motion of the left hemithorax and increased tactile fremitus at the left base posteriorly. On auscultation there were occasional moist inspiratory rales over the left apex posteriorly.

Laboratory studies on admission revealed normal red blood cell count, hemoglobin, complete urinalysis and serology. The white blood cell count was 12,700 with 61 per cent neutrophils, 35 per cent lymphocytes and 4 per cent eosinophils. Kidney function tests were normal. Smear of concentrate of the sputum was positive for tubercle bacilli on November 22, 1953 and the culture of that specimen was negative.

Chest x-ray film on November 5, 1953 revealed thickening of the pleura along the left lung peripherally. There was chronic fibrous pleurisy at the left base and fibrocalcareous deposition was noted at the second rib anteriorly on the left. Planograms on November 25, 1953 showed marked pleural reaction with thickening in the left apex and along the periphery of the left lung field. Honeycombing was present in a wedge shaped area of dense fibrosis at the second rib anteriorly on the left.

It was planned to perform a resection of the involved area of the left upper lobe following three to four months of preparatory antimicrobial therapy. Streptomycin 1 gram twice weekly and para-aminosalicylic acid 12 grams daily were started on November 16, 1953. Approximately one month later he developed generalized aching, chills and temperature up to 101° F. In addition he developed an urticarial eruption with severe pruritus. It was felt that this reaction was due to streptomycin and it was therefore discontinued. Dihydrostreptomycin 1 gram was substituted for the streptomycin and three hours after the injection of the first dose on December 20, 1953 he developed a similar reaction to that following streptomycin. He received antihistaminic drugs following the reaction to streptomycin and these were continued during the time he received dihydrostreptomycin. Dihydrostreptomycin was discontinued and isoniazid (Rimifon) 300 milligrams daily was started on December 21, 1953 without para-aminosalicylic acid. Nine days after isoniazid was started, a slight icteric tinge of the sclerae was noted. Generalized pruritus, without signs of a dermatitis, also developed the same day. Isoniazid was discontinued at that time. The degree of clinical jaundice increased rapidly over the following four days and was not associated with biliary colic or fever. The stools became clay colored for a two day period. A flat plate x-ray film of the gall bladder area was normal. On physical examination there was some tenderness over the liver area and the liver edge was palpable two finger breadths below the right lower costal margin. The icteric index attained a maximum of 100 units nine days following the appearance of jaundice and gradually subsided to 16 units over a month period, at which time he was discharged from the hospital as absent without official leave. Treatment of jaundice consisted of intravenous glucose, supplemental vitamins, high carbohydrate, high protein, low fat diet.

Table I summarizes the laboratory findings throughout the period of hospitalization.

From the Veterans Administration Hospital, Tucson, Arizona.

TABLE I
BLOOD COUNTS AND LIVER FUNCTION TESTS

TESTS	DATES										
	11/18/53	12/31/53	1/4/54	1/5/54	1/6/54	1/8/54	1/13/54	1/15/54	1/22/54	1/29/54	2/5/54
Red Blood Count	5,250,000			4,600,000		4,750,000	5,300,000		4,900,000	5,150,000	5,400,000
Hemoglobin	15 gms.			14 gms.		15 gms.	15.5 gms.		14.5 gms.	15 gms.	15.5 gms.
White Blood Count	12,700			11,700		13,800	16,600		12,850	13,700	8900
Neutrophils	61			26		31	56		37	37	45
Lymphocytes	35			47		28	28		33	54	43
Eosinophils	4			25		37	14		22	1	9
Monocytes				1		4	2		7	7	3
Basophils				1					1	1	
Van den Bergh											
Direct		Strongly Positive									
Indirect		5.4 mg. %									
Thymol Turbidity		6.5 Units				8 Units		7.5 Units	6.5 Units	3.5 Units	4.5 Units
Cholesterol and			Total 172 mg. %								
Cholesterol Esters			Esters 125 mg. %								
Icteric Index			97.5 Units			100 Units		43.5 Units	31 Units	23 Units	16 Units
Cephalin *Flocculation*			3+ (48 hours)								
Total Protein				8.7 gms.							
Albumin				3.2 gms.							
Globulin				5.5 gms.							
Sedimentation Rate	3mm/hr.			5mm/hr.							
Bleeding Time				1 min. 16 sec.							
Prothrombin *Time*				23 sec. 14 sec. control		20 sec. 14 sec. control		17 sec. 14 sec. control	15.5 sec. 14 sec. control		
Urinary *Urobilinogen*					0.40 Ehrlich U/2 hr.						
Alkaline Phosphatase					12.5 Units						

Comment

The cause of the hepatitis and jaundice in this case has several possibilities. Our patient developed allergic reactions to both streptomycin and dihydrostreptomycin which had completely subsided prior to starting isoniazid. Jaundice developed nine days after isoniazid was begun and we feel that this drug was responsible for the hepatitis rather than streptomycin and/or dihydrostreptomycin. We feel that homologous serum jaundice can be excluded on the basis of lack of parenteral injections in the period 60 to 120 days prior to the onset of jaundice. Infectious hepatitis cannot be definitely ruled out, although the marked eosinophilia and absence of fever makes this possibility unlikely. Extrahepatic obstruction was not considered as an etiological factor as evidenced by lack of biliary colic, lack of Charcot fever reaction, failure to demonstrate biliary calculi and by the liver function studies which supported a diagnosis of hepatocellular damage.

SUMMARY

A case of hepatitis and jaundice in a patient treated with isoniazid is reported.

SUMARIO

Se reporta un caso de hepatitis e ictericia en un paciente tratado con isoniacida.

RESUME

Les auteurs rapportent un cas d'hépatite avec ictère chez un malade traité par l'isoniazide.

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A New Method for Producing Pleural Symphysis in Spontaneous Pneumothorax

REPORT OF A CASE TREATED WITH STREPTOKINASE-STREPTODORNASE

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The principle of preventing recurrence of spontaneous pneumothorax by means of obliterative pleuritis is not new. Many substances have been employed to bring about an inflammatory pleural reaction. They include silver nitrate and dextrose solutions, iodine, iodoform, hypertonic saline, talcum powder and the patient's own blood. Beardsley et al,[1] in their comprehensive paper on spontaneous pneumothorax, recommended scrubbing of the visceral and parietal pleurae with gauze in order to produce adhesion between these surfaces. Other surgical procedures advocated in the literature for treatment of spontaneous pneumothorax range from excision of a solitary cyst or bleb to complete removal of the affected lung. Water-sealed drainage is also widely used.[2]

In searching for an alternative method of promoting pleural adhesion in recurrent, non-hemorrhagic spontaneous pneumothorax, the writer considered the irritative properties of streptokinase-streptodornase. It was thought that the irritation of the pleurae and outpouring of fluid which follows the instillation of these enzymes into the pleural cavity could be utilized to obtain secure attachment of the lung to the chest wall.

Case Report

F. W., a 36-year-old male, was admitted to Löt Sanatorium on October 1, 1953. Seven weeks previously he had complained of sharp pain in the right side of the chest and spontaneous pneumothorax was roentgenographically diagnosed. On admission the roentgenogram showed the base of the right lung to be so concentrically collapsed that it was drawn up clear of the diaphragm. The right upper lobe was prevented from total collapse by an apical adhesion. Six similar episodes of right spontaneous pneumothorax had been confirmed over the last 20 years. Spontaneous collapse of both lungs had occurred in 1952. In all of these episodes the treatment had consisted of bed rest with or without aspiration of the pleural air.

Thoracoscopy was performed on October 7, 1953 and the surface of the right lung inspected. The upper lobe was attached to the parietal pleura by a sail-shaped adhesion. This lobe was normal in color and on its surface were many small blebs. The parietal pleural surface was painted with a 2 per cent solution of silver nitrate after local painting with xylocain. The patient experienced no discomfort during or after this procedure, apart from a rise in temperature to 38.3° C. A small pleural effusion formed, but despite this and intermittent aspiration of air the middle and lower lobes remained totally atelectatic for several weeks.

On November 18, 1953, when the atelectasis had begun to show signs of clearing, 20,000 units of varidase** were instilled into the right pleural cavity. After about 16 hours the patient's temperature rose to 39° C. Fluoroscopy then showed a small pleural effusion and the pleural cavity was washed out with normal saline solution. Continuous suction drainage with negative pressure of 6 to 8 cm. of water was instituted and maintained for one week. At the end of this period the lung had re-expanded and adhesions had formed which divided up the lower pleural space. For this reason evacuation of pleural fluid necessitated intermittent needling at different sites.

*Physician-in-Chief, Löt Sanatorium, Strängnäs, Sweden.

**Streptokinase-Streptodornase *Lederle*.

Following removal of the varidase by pleural irrigation his temperature fell to 37.5° C. As the fluid re-formed and increased, however, the temperature gradually rose again until on November 4 it reached 39.2° C. It then fell slowly and by the end of December he was afebrile. When he was discharged home on January 30, 1954 the right lung was almost completely adherent to the parietal pleura. The basal parts of the lung, however, showed comparatively poor re-expansion (Figure 2), possibly due to the long periods of atelectasis and to the obliteration of the costophrenic sulcus which had commenced before varidase treatment was instituted (Figure 1). During the entire period of treatment he was encouraged to perform deep abdominal breathing and to lie as much as possible on the healthy side so as to keep open the costophrenic sulcus of the treated side. Figures 2 and 3 show the pulmonary condition 7 months after treatment. The diaphragmatic mobility is surprisingly good.

Discussion

In this case of recurrent spontaneous pneumothorax with extensive formation of emphysematous blebs on the surface of the lung, varidase was tested as a means of producing obliterative pleuritis. Instillation of 20,000 units brought about a general pleural irritation, which on the first day was accompanied by a rise in temperature but little fluid formation. The subsequent pleural effusion reached its maximum after about 6 days. That the parietal pleura in its entirety was involved in this reaction was shown by the appearance on the roentgenograms of an inflammatory swelling 3 mm. in depth. The lung was gradually re-expanded by continuous suction drainage of the pleural contents. As the adhesions formed the fluid became loculated, which made aspiration somewhat difficult.

It is not suggested that the dosage of varidase employed in this case was optimal. Since varidase appears to effect a generalized irritation of the pleural surfaces lower dosage may suffice. This extensive reaction is, in the writer's experience, in contrast to that of silver nitrate solution, which often produces adhesion only over the areas painted.

If it is desired to bring about adhesion of the basal parts of the lung before e. g. extrapleural pnemothorax, it should be kept in mind that a partial inhibition to varidase develops with repeated use. This is par-

FIGURE 1

FIGURE 2

Figure 1: Right spontaneous pneumothorax occurring for the 7th time in a 36-year-old man. Obliteration of the right costophrenic sinus has commenced. The arrows indicate the boundary of the lung at the site of an emphysematous portion.—*Figure 2:* The same patient 7 months after intrapleural instillation of varidase and suction drainage.

ticularly important in cases in which varidase may be required to facilitate postoperative removal of clots. In sensitive patients the possibility of an anaphylactoid reaction secondary to the use of streptokinase-streptodornase, such as described by Orr Goehring and Grant,[3] must be kept in mind.

Intrapleural instillation of varidase is not recommended for simple cases of non-hemorrhagic spontaneous pneumothorax, which do well with such methods as suction drainage. But in patients with a history of repeated pulmonary collapse, particularly when the surface of the lung shows extensive emphysematous blebs, the method merits consideration.

Warning must be given, however, against injudicious dosage of varidase which, by causing an excessive pleural reaction, may ultimately lead to a condition requiring pulmonary decortication.

SUMMARY

Past and current methods of treating spontaneous pneumothorax are briefly reviewed, and a case is presented in which pleural obliteration was achieved by intrapleural instillation of varidase (streptokinase-streptodornase). The patient was a 36-year-old man with a 20-year history of recurrent episodes of non-hemorrhagic spontaneous pneumothorax.

Varidase appears to evoke generalized pleural irritation. With judicious dosage and continuous suction drainage and breathing exercises, the

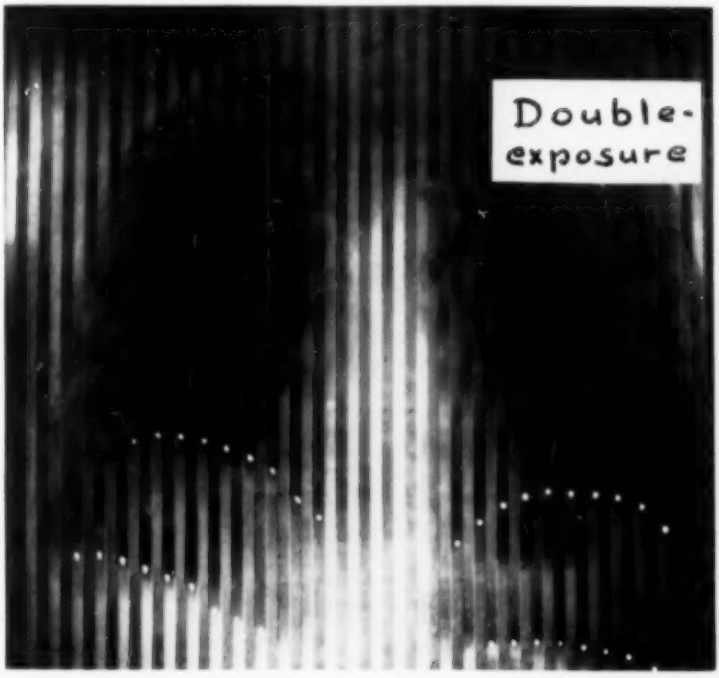

FIGURE 3: Double-exposure roentgenogram taken with the writer's mobile grid and showing the maximum inspiratory and expiratory movements of the diaphragm.

method would appear to merit trial in relapsing spontaneous pneumothorax.

RESUMEN

Brevemente se revisan los métodos del pasado y del presente para el tratamiento del neumotórax espontáneo y se presenta un caso enel que la obliteración se logró por la instilación intrapleural de varidasa (estreptoquinasa-estreptodornasa). El enfermo era un hombre de 36 años con episodios recurrentes de neumotórax espontáneo recurrente no hemmorrágico. La varidasa parece provocar una irritación pleural generalizada.

Con una dosificación juiciosa drenaje con aspiración y ejercicios respiratorios, el método parece merecer el ensayo en el neumotórax espontáneo recurrente.

RESUME

L'auteur fait la revue rapide des méthodes de traitement du pneumothorax spontané qui ont été utilisées dans le passé, et celles que sont actuellement en cours. Il présente un cas dans lequel l'instillation intrapleurale de "varidase" (streptokinase-streptodornase) a permis la symphyse pleurale Le malade était âgé de 36 ans. Il avait un passé de 20 ans de rechutes de pneumothorax spontanés non hémorragiques. La "varidase" semble provoquer une irriation pleurale généralisée Cette méthode semble devoir être utilisée pour traiter les pneumothorax spontanés à condition qu'oon lui associe une aspiration continue et judicieusement dosée, ainsi que des exercices respiratoires.

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2 Briggs, J. N., Walters, R. W. and Byron, F. X.: "Spontaneous Pneumothorax," *Dis. Chest*, 24:564, 1953.

3 Orr Goehring, W. and Grant, J. J.: "Allergic Reaction to Streptokinase-Streptodornase Solution Given Intrapleurally," *J.A.M.A.*, 152:1429, 1953.

Teaching Chest Disease
House Staff Chest Conference

ROBERT R. SHAW, M.D., F.C.C.P.*
Dallas, Texas

A chest x-ray conference has developed in our hospital that has become one of the most enthusiastically attended teaching sessions for the house staff. The conference was initiated by the house staff and is conducted by them. The success of the conference seems to come from the informal manner of its conduction, the appeal of participation, and the fact that it is meeting a need expressed by the staff itself.

The teaching material that forms the basis for discussion at these conferences is drawn from the patients having chest disease who have been treated on the section of thoracic surgery during the preceding week. No attempt is made to limit the time of discussion of the problem presented by any particular patient, since in the course of time a broad cross section of problems presented by patients having chest disease will be encountered. The only choice of material that is attempted is to present the more interesting and unusual conditions at the first part of the weekly session. This is followed by more routine material if time is available.

The meeting is conducted by the resident in thoracic surgery and a radiological resident. It is an x-ray quiz type of conference in which the residents quiz the other residents and interns attending the conference. The attending staff members remain in the background and take part in the discussion only when a direct question is put to them or when they feel that some point should be made that has been overlooked. The house staff member who is being quizzed is asked to make an objective reading of the films presented for discussion. He is then required to give a differential diagnosis suggested by the appearance of the films. The history and laboratory findings are then made available to him to aid him in narrowing down the diagnosis. Following this, the true diagnosis, which usually has been arrived at through surgery, is disclosed. Finally, comments on the etiology of the particular condition and the manner of treatment are made.

The conference developed through the request of the Department of Radiology to the resident in thoracic surgery that they have the opportunity to see the roentgenograms taken of patients in the course of their work-up prior to surgery. Very often these roentgenograms have been made in outside clinics. They decided to have a weekly session in order to review this material. Medical residents learned that these sessions were being held and asked that they be allowed to attend. Soon the surgical residents and the interns were added to the group. Still later the resident in thoracic surgery said that the group thought the sessions would be

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The ninth in a new series of articles prepared under the sponsorship of the Council on Undergraduate Education of the American College of Chest Physicians.

more valuable if at least one attending staff member from the Division of Thoracic Surgery and one from the Department of Radiology would also attend. Since the conference is held immediately preceding the weekly surgical rounds, many of the members of the Division of General Surgery now attend the conference.

Much of the enthusiasm in the conference is generated throughout the week by a bantering attitude on the part of the residents. It is common when they see an interesting roentgenogram of the chest to exclaim, "Oh Boy! Wait until I catch Dr. So and So on this case." This competitive attitude continues during the conference itself and does a great deal to enliven it.

Occasionally there will be a request from the house staff for a specific teaching session in which a particular radiological technique is explained to them. The director of the Department of Radiology during one session discussed angiocardiograms and their interpretation. Bronchograms and their interpretation have also formed the basis for a special session. Such presentations are held, however, only on the request of the house staff.

A teaching session which is initiated by the house staff and conducted by the house staff for their own interest is conducive to effective teaching. The use of current clinical material eliminates much of the drudgery of preparation for the sessions and is seldom repetitious. A firm policy of leaving the control of the conference in the hands of the house staff and limiting the amount of participation by the attending staff seems to work toward preserving enthusiastic attendance and participation.

INTERIM SESSION

The Interim Session of the College will be held at the Sheraton Plaza Hotel, Boston, Massachusetts, November 27 and 28, 1955. The Board of Regents and Board of Governors will meet on Sunday, November 27, and a scientific program will be presented at the hotel on Monday, November 28, sponsored by the New England States Chapter of the College. Dr. Richard H. Overholt, Boston, Chairman of the Committee on Scientific Program, has announced that the complete program will be available for publication in the next issue of the College journal.

Examinations for Fellowship in the College will be given at the Sheraton Plaza Hotel on Saturday, November 26, under the direction of Dr. Harold G. Trimble, Oakland, California, Chairman of the Board of Examiners.

The Clinical Meeting of the American Medical Association will be held in Boston, November 29-December 2. Members planning to attend these meetings are requested to write directly to the Sheraton Plaza Hotel for reservations. Please indicate that you are attending the meeting of the American College of Chest Physicians and give arrival and departure dates.

LOUIS MARK MEMORIAL LECTURESHIP ESTABLISHED

The Committee on Lectureships of the American College of Chest Physicians announces establishment of the Louis Mark Memorial Lecture. The first lecture will be presented at the 22nd Annual Meeting of the College to be held at the Sherman Hotel, Chicago, Illinois, June 7-10, 1956. This lectureship was made possible by a grant of $10,000.00 by the widow, Mrs. Fanny Mark of Columbus, Ohio.

College Chapter News

PACIFIC NORTHWEST CHAPTER

The Pacific Northwest Chapter of the College will meet jointly with the Trudeau Society, November 4 and 5 at the Tuberculosis Auditorium of the Willow Chest Centre, Division of Tuberculosis Control of British Columbia in Vancouver. The following program will be presented:

November 4

9:00 a.m. Registration
"The Shoulder Arm Syndrome"
H. Robinson, Vancouver
"Forty Cases of Lung Abscess"
George Bogardus, Seattle, Washington
"Visuals as Tools in Medical Presentation"
Knute Berger, Seattle, Washington
"The Appearance of Tuberculosis in Vaccinated Indian Children"
Carl R. McKinnon, Vancouver, B. C.
Business meeting, College chapter
12:30 Luncheon (White Spot Restaurant)
2:00 p.m. "Biopsy of Diffuse Pulmonary Diseases
John E. Tuhy, Portland, Oregon
"Diffuse Pulmonary Actinomycosis"
Jorma M. Leinassar, Portland, Oregon
"Decision for Surgery"
Herbert S. Stalker, Vancouver, B. C.
X-ray Conference
7:00 p.m. Dinner—Faculty Club, University of British Columbia

November 5

9:00 a.m. "Management of Chylothorax"
Chester W. Moen, Seattle, Washington
"Cardiovascular Surgery"
Gordon L. Maurice, Portland, Oregon
"Non-penetrating Chest Injuries"
W. Elliott Harrison, Vancouver, B. C.
"Pneumoperitoneum as an Aid in Re-expansion Following Pulmonary Resection"
Malcolm L. Allan, Vancouver, B. C.

"Staphylococcal Pneumonia and Empyema"
George D. Saxton, Vancouver, B. C.
"Correlation of Pulmonary Disease with Pre-operative X-ray"
E. A. Gee, Tranquille, B. C.

SOUTHERN CHAPTER

The annual meeting of the Southern Chapter, which includes the 16 southern states and the District of Columbia, will be held at the Shamrock Hotel, Houston, Texas, November 13 and 14. Dr. Robert E. Schwartz, chairman of the program committee, has announced that the following program will be presented:

Sunday, November 13

9:00 a.m. Registration

9:30 a.m. Scientific session—Daniel E. Jenkins, Houston, Texas, Chairman—medical section, presiding:
"Patient Adjustment to Hospitalization for Tuberculosis"
L. J. Moran. Ph.D., G. W. Fairweather, Ph.D., R. V. Morton, Ph.D., and L. S. MacGaughran, Ph.D., Houston, Texas
"Atypical Acid Fast (Chromogenic) Organisms Complicating Pulmonary Disease"
Lt. Hyman Florence, Fort Sam Houston, Texas
"X-ray Radiation Therapy of Middle Lobe Collapse Found in Children"
Hurst B. Hatch, Jr., New Orleans, Louisiana
"Management of Respiratory Problems in Chronic Poliomyelitis"
Milton V. Davis, Dallas, Texas

12:00 noon Round table luncheon—"Cor Pulmonale"
Moderator: Daniel E. Jenkins
Panel members: J. Pervis Milnor, Jr., Memphis, Tennessee and William F. Miller, Dallas, Texas

2:00 p.m. Scientific session—Lawrence H. Strug, New Orleans, Louisiana, Chairman—surgical section, presiding:
"Mediastinal Tumors: An Analysis of 135 Cases"
Capt. Thomas G. Nelson, Lawrence M. Shefts, and Col. Warner F. Bowers, San Antonio, Texas
"Aspergilloma"
John S. Harter, Louisville, Kentucky
"Tracheotomy, Indications, Technique, and After-Care"
R. M. Shepard, Jr., Tulsa, Oklahoma
"Hernia Through Foramen of Morgagni"
Claude C. Craighead, New Orleans, Louisiana
"Diagnostic Conference"
Walter J. Stork, Houston, Texas, Moderator

6:00 p.m. Social Hour, Doctors Club

7:00 p.m. President's Banquet, Doctors Club
President's Message—George R. Hodell, Houston, Texas

8:15 p.m. The Paul Turner Lecture
"Clinical Aspects of Pulmonary Mycotic Infections"
Michael L. Furcolow, Kansas City, Kansas

Monday, November 14

9:00 a.m. Scientific session—Alfred Goldman, St. Louis, Missouri, presiding:
"Importance of the Pulmonary Nodule"
Donald L. Paulsen and Robert R. Shaw, Dallas, Texas
"Objective Data Relative to the Role of the Vagus Nerve in Pulmonary Emphysema of the Hypertrophic Type"
Osler A. Abbott, W. E. Van Fleit, and F. L. Mendez, Atlanta, Georgia
"Problems in Management of Cor Pulmonale"
William F. Miller, Dallas, Texas
"Pulmonary Sarcoidosis"
Major Lloyd J. Gregory, Jr., Denver, Colorado

12:00 p.m. Business Meeting Luncheon

Professor and Mrs. Ludwig Heilmeyer with some of the members of the Japanese Chapter of the College in Tokyo.

NEWS NOTES

Professor Ludwig Heilmeyer, Director of the Medical Clinic, University of Freiburg, Germany, and Governor of the College for the state of Würtemberg-Baden, together with Mrs. Heilmeyer, recently concluded a lecture tour in the Far East. During his tour, Professor Heilmeyer presented a series of three lectures before the East India Chapter of the College in Calcutta and spoke before members of the South India Chapter of the College in Madras on "New Investigations Regarding the Dynamics of the Heart."

Professor Heilmeyer also visited Japan at the invitation of the 14th Japanese Medical Congress held in Kyoto, April 1-5. A special meeting of the Japanese Chapter of the College was held for Professor Heilmeyer in Tokyo which was attended by more than 500 physicians.

Dr. Fred M. Meixner, Peoria, Illinois, one of the pioneer workers in the fight against tuberculosis, was honored during the 50th anniversary of the Illinois Tuberculosis Association held in Peoria recently.

Dr. Hurley L. Motley, Los Angeles, California, and **Dr. Maurice S. Segal,** Boston, Massachusetts, have received grants from the Tobacco Industry Research Committee for research projects. Dr. Motley's project is "A study of the effects of smoking on pulmonary function" and Dr. Segal is studying the "Effects of cigarette smoking on normal subjects."

Dr. Miguel Canizares, Director of the Quezon Institute, Quezon City, Philippines, was recently awarded the Achievement Medal and Diploma of Honor "in recognition of his valuable services contributed to clinical medicine and to the people of the Philippine Islands." The award was made by the President of the Philippines, Raul Magsaysay, at the meeting of the Philippine Medical Association.

Dr. Nathaniel E. Reich, Brooklyn, New York, presented a series of lectures on cardiovascular diseases in the Near East during August. Dr. Reich spoke under the sponsorship of the College chapters at the medical schools of the University of Athens, the University of Cairo, and at the Hebrew University in Jerusalem.

Dr. Elmer F. Herring, San Fernando, California, has been appointed Director of the Tuberculosis Control Division of the Los Angeles City Health Department. Dr. Herring was formerly tuberculosis control officer for the Veterans Administration Hospital, San Fernando.

Dr. J. Winthrop Peabody, Sr., Washington, D. C., was recently elected President of the Pan American Medical Society of the District of Columbia.

INTRODUCING THE OFFICIALS OF THE FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

(Mueller Photo, Chicago)

HONORARY PRESIDENT
Chancellor Konrad Adenauer

(Schafer Photo, Wuppertal-Elberfeld)

PRESIDENT
Professor Gerhard Domagk

VICE PRESIDENT
Professor H. W. Knipping

SECRETARY GENERAL
Professor Josef Jacobi

EXECUTIVE COMMITTEE

Honorary Members

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Director, Department of Health, Ministry of the Interior

Doctor Ernst Schwering
Mayor, City of Cologne

Doctor Max Adenauer
Director, City of Cologne

Chairman, Professor Joachim Hein, Regent
Tönsheide/Schleswig-Holstein

Professor Ludwig Heilmeyer, Freiburg
Governor for Württemberg-Baden

Professor Josef Jacobi, Hamburg
Governor for Hamburg, Schleswig-Holstein and Bremen

Professor H. W. Knipping, Cologne
Governor for Nordrhein-Westfalen

Professor Rudolph Schoen, Göttingen
Governor for Neidersachsen

Professor Walter Unverricht, Berlin
Governor for Berlin

Professor E. Wollheim, Wurzburg
Governor for Bavaria

Professor Hans Wurm, Weisbaden
Governor for Rheinland-Pfalz

Professor Rudolf Zenker, Marburg
Governor for Hessen

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Professor Andrew L. Banyai, Milwaukee, Wisconsin, *Chairman*

Professor J. Ignacio Baldo, Caracas, Venezuela
Chairman, Council on Pan American Affairs

Professor Miguel Canizares, Quezon City, Philippine Islands
Chairman, Council on Pan Pacific Affairs

Professor A. Omodei Zorini, Rome, Italy
Chairman, Council on European Affairs

Professor David F. Marais, Cape Town, South Africa
Chairman, Council on African and Eastern Affairs

Murray Kornfeld, Chicago, Illinois, *Executive Director*

FOURTH INTERNATIONAL CONGRESS

The Chancellor of the German Federal Republic, Hon. Konrad Adenauer, whose portrait appears on the opposite page, has accepted the invitation to serve as the Honorary President of the Fourth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the College, which is to take place in Cologne, Germany, August 19 through 23, 1956. The Hon. Ernst Schwering, Mayor of Cologne, extends a cordial invitation to all members of the College to attend this world congress.

One of Germany's most famous scientists, Dr. Gerhard Domagk, who received the Nobel Prize for his discovery of the sulfonamides, is the President of the Congress. As is indicated on the previous page, the Fourth International Congress will be supervised by an outstanding group of scientists and statesmen in Germany which has pledged its support in the presentation of a brilliant program of scientific and social events.

The scientific program to be presented at the Congress is now being organized by the committee and physicians having carried out original work in diseases of the chest (heart and lung) which they wish to present, are invited to send outlines of their studies to Dr. Andrew L. Banyai, Chairman, Committee on Scientific Program, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A. Physicians who have motion pictures or exhibits dealing with heart and lung disease are also requested to submit complete data to the Committee. All requests for places on the scientific program will be given due consideration.

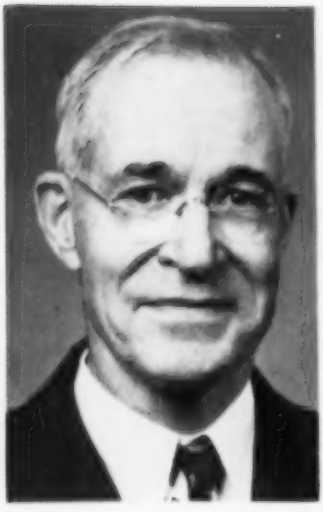
The City of Cologne, which will be host to the Fourth International Congress, lies in the land of "black diamonds," the German federal state of North-Rhine-Westphalia, wherein one of the largest coal reserves in Europe is to be found. With over half a million inhabitants, Cologne is the cornerstone of the Rhine-Rhur area and the trade metropolis of the entire western territory, as it had been as a Roman city under the name of "Colonia Aggripina." The precious works of art and monuments preserved for more than two thousand years are still extant, so that Cologne may rightly be called a treasure-house of Europe. The Cologne Cathedral, pictured below, is one of the landmarks of Germany and a main attraction for Rhine tourists. Another great attraction, of course, is the beautiful Rhine River and Cologne is the best starting point for a trip up the Rhine which for centuries has been a delightful experience to travelers. Large fairs and exhibits are important factors of modern economic life in Cologne, and both producers and traders meet there. Cologne is an important medical center and is particularly well fitted for this world congress on diseases of the chest.

The International Travel Service, Inc., Palmer House, Chicago, Illinois, has been appointed the official travel agent for the Congress and they are presently engaged in organizing several tours which will be announced to the membership in the near future.

The Cathedral of Cologne

Obituary

ROBERT KELLOGG CAMPBELL
1880-1954



Dr. Robert Kellogg Campbell, a past Governor of the College for the State of Illinois and Chairman of the Board of Governors, died on November 12, 1954, of a cerebral hemorrhage, at age 74. This familiar figure in the professional and fraternal life of Illinois had been forced into retirement in April 1949 because of arterio-sclerotic heart disease.

His passing has left those of us who knew him well with a deep feeling of loss and sadness. There is the urge to eulogize him to the fullest, but his inherent modesty admonishes me to keep it brief and to the point.

Dr. Campbell was born in Springfield, Illinois, August 1, 1880, where he spent the early part of his life and obtained his primary education.

His pioneering spirit was exemplified at an early age by traveling with his father to Roseburg, Oregon in a springboard wagon first to the Dakotas, and then with the team and wagon aboard a freight train to Oregon. It was there that he explored the field of law at his father's suggestion by reading and working in a law office. His interest soon turned to farming and studying medicine. After farming for two years, he enrolled at St. Louis College of Physicians & Surgeons from which he graduated with honors in 1908. He served as an externe at the University Hospital during his senior year and as an interne the following year. He entered general practice for a short time in Missouri and then returned to Springfield to serve as "City Physician" for several years. He then opened an office in a nearby rural community—Waggoner, Illinois.

While serving this rural community and combating many epidemics and much mud, he continued to be a student, interested in the newer fields in medicine. It was while studying roentgenology at St. John's Hospital that he became acquainted with the Medical Director of St. John's Sanatorium & Crippled Children's Hospital which had been opened a year or two before, by the Hospital Sisters of St. Francis.

From 1921, he served as a part-time physician at this institution and this marked the start of his interest in tuberculosis and crippled children's work. In 1927, at the death of the first medical director, he discontinued his rural practice and became medical director of this institution. He served in this capacity until retirement in April 1949.

His interest and participation in College affairs led to his appointment to the Board of Governors where he served several terms, and was Chairman for one year. It was through his efforts as Governor that the first Chapter of the College was organized on May 21, 1940, for the State of Illinois. He served as the 1st President for the Illinois Chapter.

He also actively participated in many civic and fraternal organizations. He was a 50 year Mason, a member of Knights Templar, the Shrine and High Twelve Club. He was a member of the Springfield Rotary Club for 25 years and the Elks Club over 30 years.

Dr. Campbell's cheerful disposition, optimistic outlook on life, understanding of human nature, and keen sense of humor endeared him to those about him. In his professional work he was open-minded, progressive and he traveled widely and frequently to remain up to date in the treatment of tuberculosis.

Modesty and good will predominated his character. He signed almost all of his letters "Fraternally yours," and he meant it!

DARRELL H. TRUMPE, M.D.
Governor

Obituary

DAVID W. HEUSINKVELD
1897 - 1955

Dr. Heusinkveld was born July 17, 1897, in Fulton, Illinois. His father was Henry J. Heusinkveld, M.D. (University of Michigan Medical College, 1883) and his mother Alice Munneke Heusinkveld, schoolteacher. All four grandparents were born and reared in The Netherlands. He was sixth in a family of ten children, eight boys and two girls, seven of whom are still living. One brother is a practicing physician in Clinton, Iowa.

He attended Hope College, Holland, Michigan, and while in attendance there had military training S.A.T.C. at Ft. Sheridan. Being commissioned 2nd Lieutenant, Infantry, he was assigned to duty at the University of Cincinnati. After his wartime experience he entered the University of Chicago, receiving a B.S. in 1921. He then attended Rush Medical College, from which he was graduated in 1924. His education at Rush was interrupted after the junior year for one year, to fill a research appointment in pharmacology at the University of Wisconsin, where he studied trypanosomiasis in white rabbits and syphillis in rats. After graduation from Rush he came to Cincinnati for a rotating internship at Cincinnati General Hospital.

Following his hospital training he became associated in the practice of Internal Medicine with Dr. Kennon Dunham and Dr. John H. Skavlem. Later this firm became Drs. Skavlem, Heusinkveld and Plessinger.

In 1934 he was appointed instructor in the faculty of the College of Medicine, University of Cincinnati and later became Assistant Clinical Professor of Medicine. He was attending physician in medicine at Good Samaritan, Bethesda and Dunham Hospitals.

In 1939 Dr. Heusinkveld was elected to the Board of the Cincinnati Anti-Tuberculosis League, and served this organization in various capacities from that time until his death, when he was Chairman of the Christmas Seal Committee (a post held for eight years), member of the Executive and Finance Committees and of the Medical and Program Committees. He was president of the A.T.L. for three years, 1945-48. In 1941 he went to New York City to study their methods of case reporting from clinical records. As a result of this study, the A.T.L. purchased for the City Health Department a photo-roentgenogram unit using 4 by 5 film. In 1944 the A.T.L. initiated its industrial health program under Dr. Heusinkveld's leadership. The first mass chest survey x-rays were done through this program.

He was a Fellow of the American College of Chest Physicians and served that organization as Ohio Governor since 1950. He was a charter member of the Ohio Trudeau Society and served as President of the Ohio Tuberculosis Association 1953-54. He had been a member of the National Tuberculosis Association and of the American Trudeau Society since 1940.

Dr. Heusinkveld served as President of the Hamilton County Medical Society in 1948-49. For five years Dr. Heusinkveld served as a member of the Council of the Ohio State Medical Association representing the First District. He was named President-Elect at the annual meeting in 1954, and took office as President April 22, 1955, when the convention was held in Cincinnati.

In addition to his widow, Dr. Heusinkveld is survived by two sons, David W. Heusinkveld, Jr., M.D., Salt Lake City, Utah, and Kennon D. Heusinkveld, New York City, New York.

Dr. Heusinkveld died suddenly and entirely unexpectedly of coronary thrombosis June 25, 1955, in Columbus, Ohio, while in attendance there of official duties as President of the Ohio State Medical Association. He died at the height of accomplishments and recognitions, respected and beloved by family, colleagues, patients, and friends. He possessed an innate talent in the art of medicine, expressed particularly by his ability to care for patients in bed for long periods of time and keep them happy. For me a happy association with deep respect of twenty-eight years in medical practice is broken.

John H. Skavlem, M.D.

ANNOUNCEMENTS

The University of Illinois College of Medicine, Chicago, will present a postgraduate course on Bronchoesophagology, under the direction of Dr. Paul H. Holinger, October 24-November 5. Information may be secured from: Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

New York Medical College Flower and Fifth Avenue Hospitals announces a postgraduate course in Pediatric Allergy, under the direction of Dr. Bret Ratner. The course consists of 30 sessions held Wednesdays, November 2 through May 31, 1956. Applicants must be certified in pediatrics or have the requirements for certification. Apply to: Office of the Dean, New York Medical College, Fifth Avenue at 106th Stret, New York 29, New York.

BOOK REVIEWS

"AN OUTLINE OF PRESENT DAY THORACIC SURGERY"
by Robert I. Carlson, Educational Publishers, Inc., St. Louis, Missouri, 1954.

This book is exactly what it purports to be—an outline of present day thoracic surgery. It presents a very complete outline of the various diseases and surgical procedures amenable to thoracic surgery. It is presented in very brief abstract form, just like the notes a medical student would take while listening to carefully prepared lectures. The bibliography is very satisfactory for those who wish to investigate further any particular field. It is not a book that would be helpful for experienced thoracic surgeons or one from which one could gain a complete picture of any diseased process or operative procedures.

Francis M. Woods, M.D.

"UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN"
by H. W. Knipping, W. Bolt, H. Valentin and H. Venrath, F. Henke (461 pages), Stuttgart, 1955.

Awareness of the importance of accurate diagnosis of heart disease is mandatory for all practicing physicians. For this reason, means which add to the accuracy of estimation of the extent of heart disease, pathologically as well as functionally, are of prime importance. In this respect, this volume represents an outstanding contribution. In its pages one finds a practicable, applicable and helpful discussion of pertinent items. Pointers on physical examination are duly emphasized. Clear-cut illustrations aid in the assaying of the normal and pathologic dynamics of cardiocirculatory function. This volume contains a remarkably clear exposition of fluoroscopic examination and other adjunct x-ray procedures. Ample space is devoted to cardiac problems in connection with surgical interventions, including items such as the potential risk inherent to general anesthesia, and also, various aspects of resuscitation. The tremendous amount of pioneering research work by the authors in cardiorespiratory function is well reflected by the substance of this distinguished tome. It directs special attention to congenital and acquired heart disease and to cor pulmonale. Technical details of cardiac catheterization, angiocardiography and diagnostic use of isotopes are offered by the authors with superb competence and with ideal precision.

This volume is one of the finest contributions in the field of internal medicine.

Andrew L. Banyai, M.D.

"FRUEHDIAGNOSTIK DES KARZINOMS IN DER INNEREN MEDIZINE"
by H. Franke, W. de Gruyter & Co., Berlin, 1953.

Physicians specializing in diseases of the chest will find interesting material in this book, relative to lung cancer, both primary and metastatic, and also, to mediastinal tumors. Excellent instructive diagrams enrich the text and enhance its teaching value tremendously. General comments on the causes of increased incidence of lung cancer are clearly presented and well documented.

The book is characterized by lucid and comprehensive thoroughness. Numerous fine illustrations and tables help in the clarification of the problems discussed. Generous space is given to the exposition of the general aspects of

carcinoma, including such items as chemotherapy. The text is easily readable. The bibliography is up to expectations. The index serves its purpose well. The book is a fine product of expert workmanship.

Andrew L. Banyai, M.D.

"DER HERZKATHTERISMMS BEI ANGEBORENEN UND ERWORBENEN HERZFEHLERN"
by O. Bayer, F. Logen and H. Wolter, George Thieme (Publisher), Stuttgart, 1954.

A review of cardiac catheterization in congenital and acquired heart disease is based on the experience of 800 studied cases. The result is a most impressive and informative book which can be highly recommended to those able to read scientific German.

The organization of the book is clear. 60 pages of well illustrated text are devoted to the technique, apparatus, chemical methods employed, and complications of the procedure. The presentation is lucid particularly in the discussion of pertinent hydraulic principles and formulas. All computation presently popular and several new ones are given with adequate discussion as to their significance and possible pitfalls. The technical quality of the pressure curves shown is excellent.

The subsequent 80 pages are devoted to the findings in congenital heart disease. The classification followed is essentially Abbott's although changes which more recent experiences brought upon are incorporated. The findings in patent ductus arteriosus, ventricular septal defect and interatrial septal defect are well discussed. Perhaps one might think that devoting 8 pages alone to Lutembacher's syndrome is somewhat out of proportion to the relative frequency of the anomaly. Possibly the author's special interest made for the greater emphasis. The discussion of Fallot's Trilogy (pulmonary stenosis and interatrial septal defect) and Fallot's Tetralogy are well done as are others of less common lesions.

The chapters on acquired heart disease deal mainly with mitral stenosis, mitral insufficiency, tricuspid disease and pulmonic insufficiency. As to be expected in our time, the emphasis is directed toward the evaluation for and of mitral valve surgery. Also here the discussion is of interest and clear.

The book presents an excellent summary of our present day knowledge of cardiac catheterization and acquired valvular disease. The numerous well chosen reproductions and the printing are of high quality.

Arthur Grishman, M.D.

"ROENTGEN DIAGNOSTICS"
by H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. First American Edition (Based on the Fifth German Edition). English translation arranged and edited by James T. Case, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago; Consultant in Radiology to the U. S. Marine and Passavant Memorial Hospital, Chicago; Director, Memorial Cancer Foundation of Santa Barbara; Radiologist (Therapy), Santa Barbara Cottage Hospital, Santa Barbara, California. Volume III, Thorax. Published by Grune and Stratton, New York. A volume of 1,116 pages and 1,085 figures.

This is the third of four volumes on roentgen diagnosis by Schinz, translated from the German into English by Dr. Case, and is devoted entirely to the Thorax. This encyclopedic set is enhanced by the translation of Dr. Case and his collaborators who should be congratulated for making it available to those physicians who are unable to read it in the original form.

The first section is concerned with the normal chest. Routine projections, technique, and fluoroscopy is discussed from a basic viewpoint. Special techniques as bronchography and kymography are also given consideration. Microscopic, gross, and segmental anatomy is well delineated along with an adequate explanation of normal confusing shadows, such as found in the apical region on the plain chest film.

The second section, which is the bulk of the volume, is concerned with the pathologic chest. Besides a complete discussion of diseases of the lung, there

are chapters on the trachea, bronchi, mediastinum, and diaphragm. The infectious processes, including the rare type of disease, is given wide coverage. There are over 100 pages on pulmonary tuberculosis alone. Separate chapters discuss such findings as emphysema, atelectasis, and circulatory disturbances of the lung.

The last section of the volume deals with diseases of the heart and blood vessels and includes chapters on the congenital anomalies of the heart. Angiocardiography and cardiac catheterization is also included.

The book is well illustrated with 1,085 figures, including radiographs and line drawings. The radiographs are printed in positive and are well defined. An extensive bibliography is included at the end of each chapter.

Any physician interested in the diagnosis of diseases of the chest will find this volume of valuable aid.

Morton Baker, M.D.

"PRACTICAL MEDICAL MYCOLOGY"
by Edmund L. Keeney. Charles C Thomas Company, Springfield, Illinois, 1955. American Lecture Series.

This book is compact, well written and informative. It contains within its 128 pages a brief, but exact, discussion of the salient features of the mycotic diseases affecting man, both localized and disseminated; a chapter on saprophytic fungi as allergens and another on poisonous fungi—amanita phalloides —commonly responsible for mushroom poisoning; the delayed poisonous fungi (genera Tuber, Marchella and Gyronitra esculenta); the ergot fungus, Claviceps purpurea. The scope of the book lends itself to the attention of the student of mycotic diseases preliminary to more exhaustive studies and to the general practitioner. The author is to be congratulated upon the concise manner in which he has assembled so much of value in this book. The reviewer unreservedly recommends Dr. Keeney's book, especially for the internist and general practitioner. For one especially interested in this field of medicine, I found the book delightful reading and gained a great deal of useful knowledge.

Alvis E. Greer, M.D.

"THE AUXILIARY HEART"
by W. W. Wasson, Charles C Thomas Company, Springfield, Illinois, 1953.

The "auxiliary heart" is defined as the additional forces other than that of the heart itself, which aid in both the greater and lesser circulations. The author is concerned with the anatomy, physiology and physiodynamics of the auxiliary heart of the lesser circulation. He considers the diseases of the chest which influence the lesser circulation. Any condition of the chest tending to revert to the fetal state or interfere with normal respiration creates a strain on the right heart. After 30 years of intensive study of the chest and evaluation of the lesser circulation by x-ray, he is eminently qualified to undertake this writing.

Within 180 pages including 72 clear illustrations, a successful attempt is made to visualize the microscopic anatomy of the lungs, capillary and lymphatic circulations, and the intrapulmonary air pressures. The book is well documented and contains voluminous footnotes. X-ray evaluation of the lesser circulation is particularly well illustrated. However, the discussion of all underlying causes of cor pulmonale has not been detailed or comprehensive. It consists of only five pages of discussion; whereas, a historical sketch occupies 24 pages.

The diaphragmatic syndrome is described as a group of symptoms in which the improper functioning of the diaphragm is the chief causative factor. The physiodynamics involving this structure are discussed.

The book would have profited also from the inclusion of sections related to therapy.

In spite of these few shortcomings, this book is highly recommended for the heart or lung specialist as well as the roentgenologist.

Nathaniel E. Reich, M.D.

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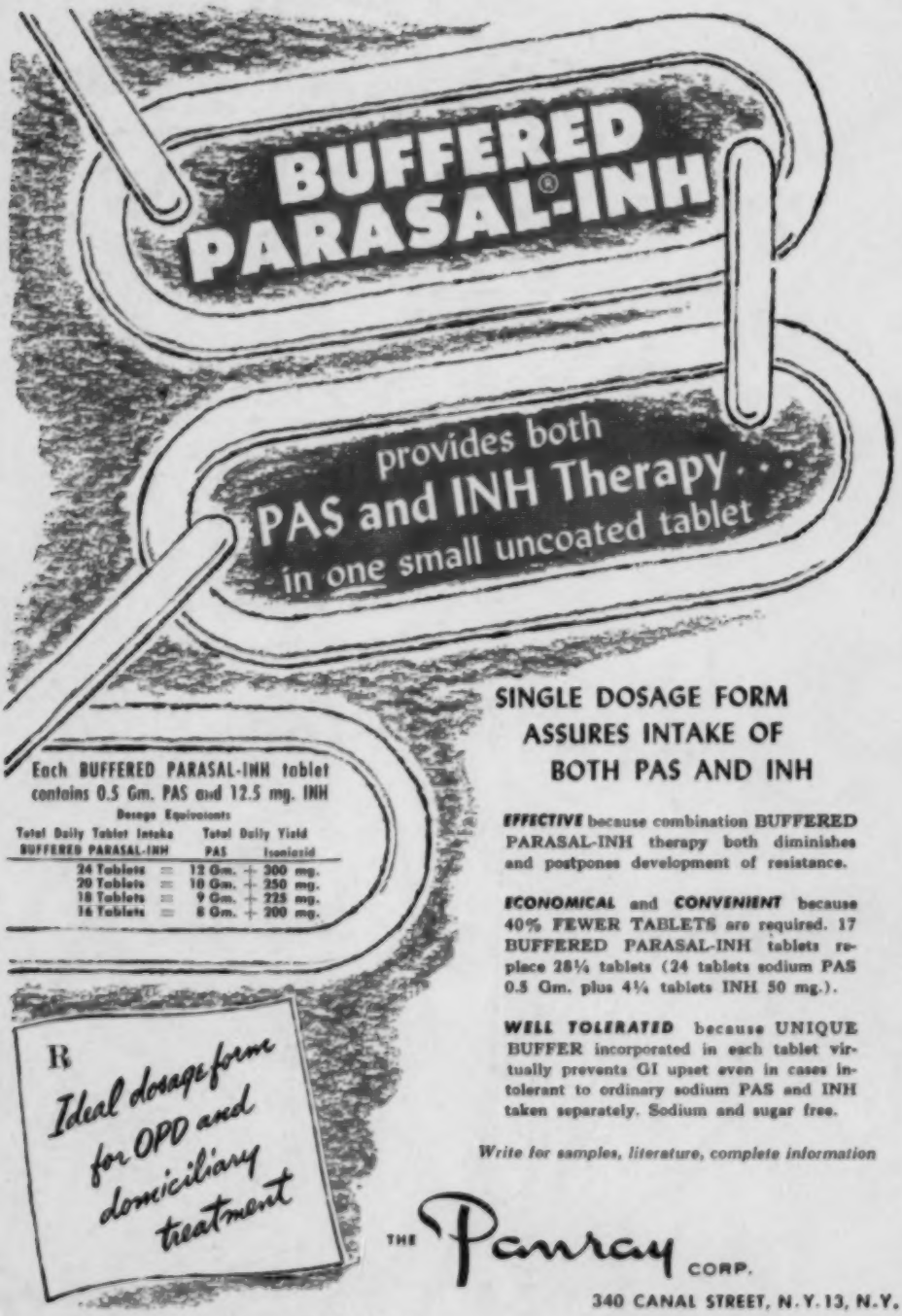

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